The Mathematics of Life

Numbers in biology and ecology

Everything is mathematical

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Rafael Lahoz-Beltra

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Preface

Life is the most beautiful and complex phenomena that exists on our planet. Since the beginning of the 20th century, biology – the study is life in all its manifestations – has become the Cinderella of other scientific disciplines. First physicists, then mathematicians, discovered a series of innovative phenomena that could be handled and described using mathematical language. Scientists such as Rashevsky, von Bertalanffy and Turing were among the first to embark upon this fruitful engagement between life sciences and mathematical formalism. Computers consolidated the quantitative study of biological problems, leading to the birth of a new discipline: biomathematics. This was put to work studying both dynamic systems – such as the workings of the brain, behaviours of ants or relationships in ecosystems – and into medical necessities – such as cancer and epidemics. Mathematical biology has therefore contributed much to advance biology – and continues to do so.

At present there are many biological and medical problems that benefit from mathematical analysis. For example, the proliferation of cancerous cells in certain classes of tumours conforms to Gompertz' law of growth. In many processes in the biotechnology industry, differential equations are required for monitoring bioreactors. Even current topical problems such as the possibility of climate change on Earth can be handled with the help of mathematical tools, such as Lorenz' climate model.

This book provides an overview of the various aspects covered by biomathematics. The first chapter discusses the main milestones and historical background. The second chapter describes the ability of mathematics to make use of differential equations to capture the dynamic essence of biological phenomena, or rather phenomena that make it possible to maintain and perpetuate life. From the demographic problems tackled by Malthus in 1798 through to the technique proposed by Libby in the 1950s for dating fossils using C-14, these types of equations have provided innumerable benefits to humanity.

However, that's not all. Mathematicians have not been able to resist the temptation of delving into a phenomenon as strange as it is fascinating – chaos. Chaos, discussed in the third chapter, is omnipresent, be it in population growth, the behaviour of share indices or the human heart rhythm. This chapter also deals with another matter related to chaos, namely fractals, in terms of their presence in nature – be it in the structure of an ice crystal or in the branches of a plant – and their graphical representation using a computer. The study of chaos and fractals brings with it the introduction of complex numbers, an understanding of which is essential in order to begin to enter into the world of fractals, even in their most pleasurable aspects.

The fourth chapter shows how mathematical biology is largely based on the use of tables or matrices, and is hence focused on operations involving matrices. The chapter concludes by using matrices to study Mendel's laws, which allows the reader to see one of the most important quantitative concepts in biology – experimental design. The fifth chapter analyses a class of mathematical objects of particular use on account of their applications – the vectors used in biomechanics, modelling neural networks and solving systems of linear equations.

This unique journey ends with the relationship between mathematics and ecology. Today, any conservation and environmental management project is impossible without a formal mathematical apparatus. Once we have defined the concept of an ecosystem, the sixth chapter will introduce us to BIDE models, a class of ecological models based on the use of matrices, which are extremely useful when it comes to the study and conservation of populations. They place a special emphasis on one of the most emblematic models from biological mathematics – the Volterra–Lotka predator–prey model. The next question that we shall tackle is at the root of a current debate: are we faced with dangerous climate change? We shall see how climate change is a problem of a 'mathematical' nature, meaning that answering this question requires sufficient knowledge of climate models and all the associated mathematical tools. The book concludes with the analysis of Daisyworld, a mathematical model devised by Lovelock in the 1980s and inspired by the Gaia hypothesis, which challenges Darwinism and the classical biological view of life.

Chapter 1

Mathematical Biology: A Historical Overview

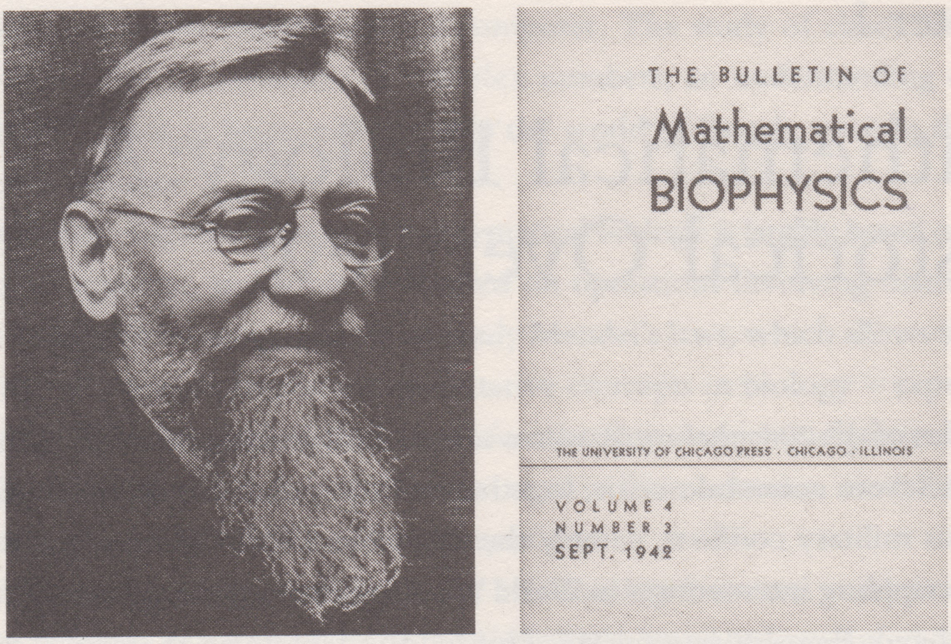
At the start of the 20th century, Russia was a political melting pot with an uncertain future. A severe economic crisis, together with popular discontent in the wake of various military conflicts, namely the disastrous 1904–1905 war against Japan and the crippling intervention in World War I against Germany from 1914, led to the Bolshevik Revolution of 1917. This led the Ukrainian theoretical physicist, Nicolas Rashevsky, now regarded as the founding father of mathematical biology, or biomathematics, to flee the country, together with his wife, Countess Emily. After travelling through various countries, the couple settled in the United States in 1924.

The birth of mathematical biology

Upon his arrival in America, Rashevsky was hired by Westinghouse research laboratories, where he researched the process known as cellular division. This was the first time the phenomenon of cell multiplication had been studied from the point of view of physics and mathematics, and was regarded as a great breakthrough at the time.

In 1934 Nicolas Rashevsky moved to the University of Chicago to take up an appointment as assistant professor in the Department of Physiology. The researcher's main contributions were published shortly after. On the one hand, there was the publication of the first scientific text on biomathematics in 1938, the famous *Mathematical Biophysics: Physico-Mathematical Foundations of Biology*, and on the other, the creation of the first scientific journal focussing on research in mathematical biology rin 1939, the original title of which was *The Bulletin of Mathematical Biology*.

However, there remained a long distance to be travelled before mathematical biology would acquire the status that it enjoys to this day, a journey that would not be without its difficulties.



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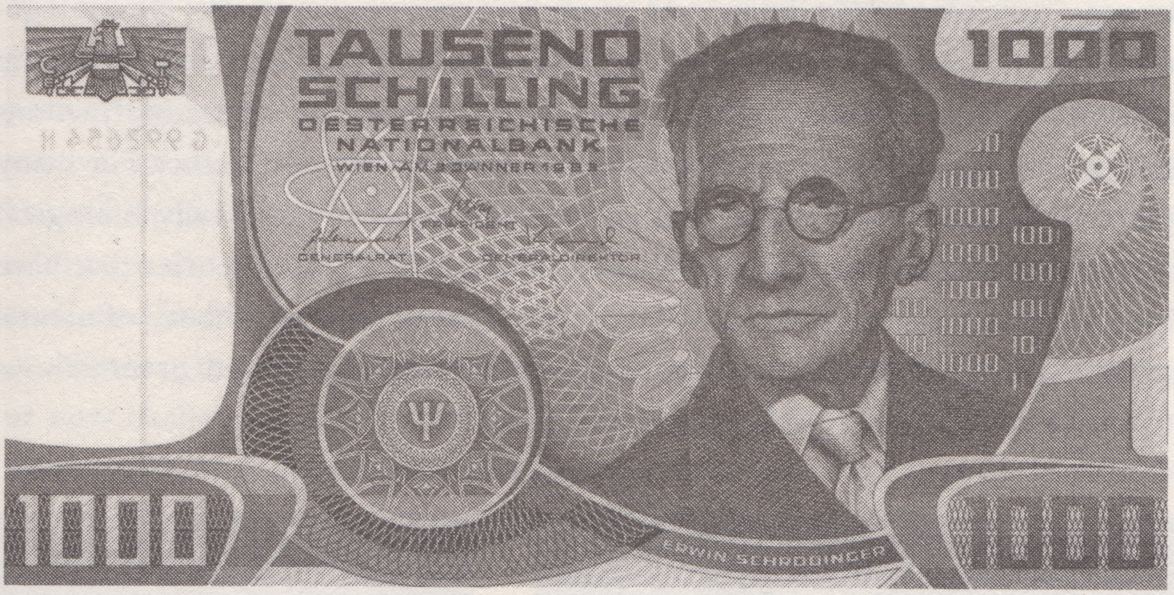
Nicolas Rashevsky (1899–1972) founded the Society for Mathematical Biology, the first journal to focus on the discipline. The publication was initially entitled The Bulletin of Mathematical Biophysics, *although it would go on to become* The Bulletin of Mathematical Biology.

Subsequently Rashevsky carried out largely theoretical research, applying set theory and propositional logic to research biological systems. His areas of interest included the study of human societies and the way in which living things appeared to organise themselves or, if we prefer, responded to a certain hierarchy. This is something that is now regarded as obvious. Consider, for example, the molecular sequence: cells → tissues → organs → systems → individual → population. Rashevsky introduced the theory of biological relations, relational biology and what he called 'organismic sets'. At the time – and arguably up to relatively recently – all these contributions passed unnoticed by the majority of life scientists, who were more interested in field and laboratory work. The real scope and usefulness of the theoretical apparatus patiently constructed by Rashevsky only became clear with the rise of what is referred to as the 'biology of complex systems', the development of which would not have been possible without one of the most important inventions in history – the computer.

The influence of physics on biology is arguably one of the most important features of this first stage of mathematical biology, which we shall refer to from now on as the founding stage of biomathematics. However, perhaps this should come as no surprise, since around 1921 Rashevsky taught the theory of relativity in Prague. In a similar way to how Einstein dedicated his final years to what he called 'unified theory', in the 1960s Rashevsky attempted to formulate his own unified theory of biology. It was a dream of formulating axioms and mathematically expressing the biological principles that governed the fascinating and complex phenomenon of life, regardless of the way in which it manifests itself, be it in plants, animals or microorganisms.

Like other contemporary physicists, such as Schrödinger, Rashevsky also posed the question: what is life? However, the Russian's dreams were cut short by a heart attack in 1972. With his death, and in spite of all the years that have passed since then, scientists have yet to find a satisfactory answer to this basic question.



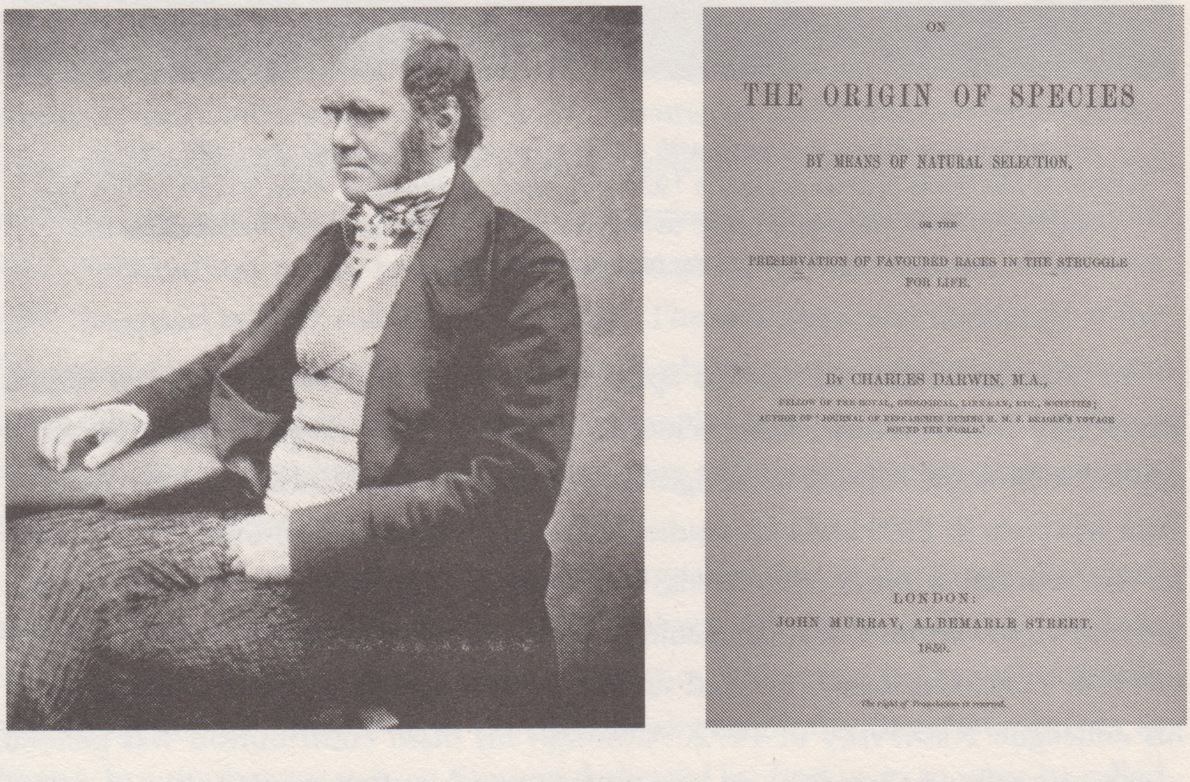
An Austrian banknote illustrated with the likeness of Erwin Schrödinger (1887–1961), winner of the Nobel prize in physics in 1933 and author of the book What is Life?, *which was published in 1944 and would go on to have an enormous influence on the development of the biological sciences.*

In contrast to the theoretical approach of mathematical biology, of which Rashevsky was a pioneer, other scientists explored a vast range of mathematics as applied to biology. Among these figures was Austrian, Karl Ludwig von Bertalanffy, who was born in 1901 and later studied at the universities of Innsbruck and Vienna; he also worked at other institutions, beginning at the University of London then moving on to various Canadian faculties, before finishing up at the State University of New York. Curiously, he died suddenly of similar causes in the same year as his colleague Rashevsky in 1972. Although his main contribution was general systems theory, which will be discussed further on, von Bertalanffy also made other important contributions to mathematical biology. Hence, in 1938, he presented his famous growth equation, now applied in fish farming to relate the size $L(t)$ of a fish to its age t (where L_K is the maximum size, L_0 the initial size and k the growth constant):

$$L(t) = L_K - (L_K - L_0)\, e^{-kt}.$$

The theory of evolution

One of the most important subjects in biology is evolution, a concept to which mathematical biology has paid considerable and well-deserved attention since its origins in the 1930s. In general terms, evolution refers to the physiological changes, amongst others, experienced by species throughout time. Over the course of millions of years, and as the result of these changes and transformations in the environment, some species survive and others become extinct. For many years, it has been known that there are various causes – specifically, biological mechanisms – that cause living things to change. Of all the theories that have been proposed, the most successful has been Charles Darwin's theory of natural selection, developed in 1859, at the height of the Victorian period, in his famous work *On The Origin of Species*.



ON
THE ORIGIN OF SPECIES
BY MEANS OF NATURAL SELECTION,
OR THE
PRESERVATION OF FAVOURED RACES IN THE STRUGGLE
FOR LIFE.

BY CHARLES DARWIN, M.A.,

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

Charles Darwin photographed at the age of 51, shortly after the publication of his revolutionary book the Origin of the Species.

According to Darwin, living things, regardless of whether they are plants, animals or microorganisms, represent possible solutions to a common problem – an adaptation to the environment. This can be related to various environments, such as a certain region of the ocean or a lake, or in the air or on land. However, there is also considerable variability within one environment, since the rainforest, an oak wood and the desert are all very different.

According to Darwin, every living thing offers a survival 'solution' to the challenges laid down by a particular environment. Those individuals with the best solution do well – in Darwin's terms they have a greater *fitness*. Fit members of a species will have a greater probability of survival and consequently greater possibilities of reaching reproductive age than the unfit ones. From the Darwinian perspective, reproduction is the goal. If an organism manages to reproduce, its survival solution, as represented by its genes, will pass to the next generation. Darwin characterised this as the fit survival traits being 'selected' by nature. If the solution is not a good fit with the habitat those 'unfit' genes die out – they are eradicated by 'natural selection'.

However, how do living things find new solutions to changes in the environment or new challenges to their survival? The answer lies in genetics, or rather in mechanisms such as mutations that alter the make-up of the genes – sometimes in a fortuitous way. To a certain extent, the greater the changes in the genes, the better possible results there will be. In this way, the individuals within a species will present a greater variety of survival solutions when it comes to changes in the environment.

The mathematical development of the theory of evolution

In the second half of the 19th century, following the publication of Darwin's work, the so-called 'English biometric school' was born, including eminent figures such as Francis Galton and Karl Pearson who began to apply statistical methods to biology. Years later, in 1930, Ronald A. Fisher, one of the greatest contributors to the development of biomathematics and biostatistics, published the 'fundamental theorem of natural selection', which uses mathematical language to explain the theory of evolution by natural selection as proposed by Darwin.

According to Fisher, under certain conditions, and over a given time t, the rhythm or speed at which the mean fitness of a given species increases is equal to the range of possible values in its genes. Representing the increase in mean fitness by $\Delta\overline{W}$, the mean fitness by $\overline{W}$ and the range of the possible values in its genes, which statisticians refer to as the genetic variance, by σ_W^2.

In mathematical biology, the previous theorem is commonly expressed as follows:

$$\Delta\overline{W} = \frac{\sigma_W^2}{\overline{W}},$$

summarising the idea stated above precisely in a single formula.

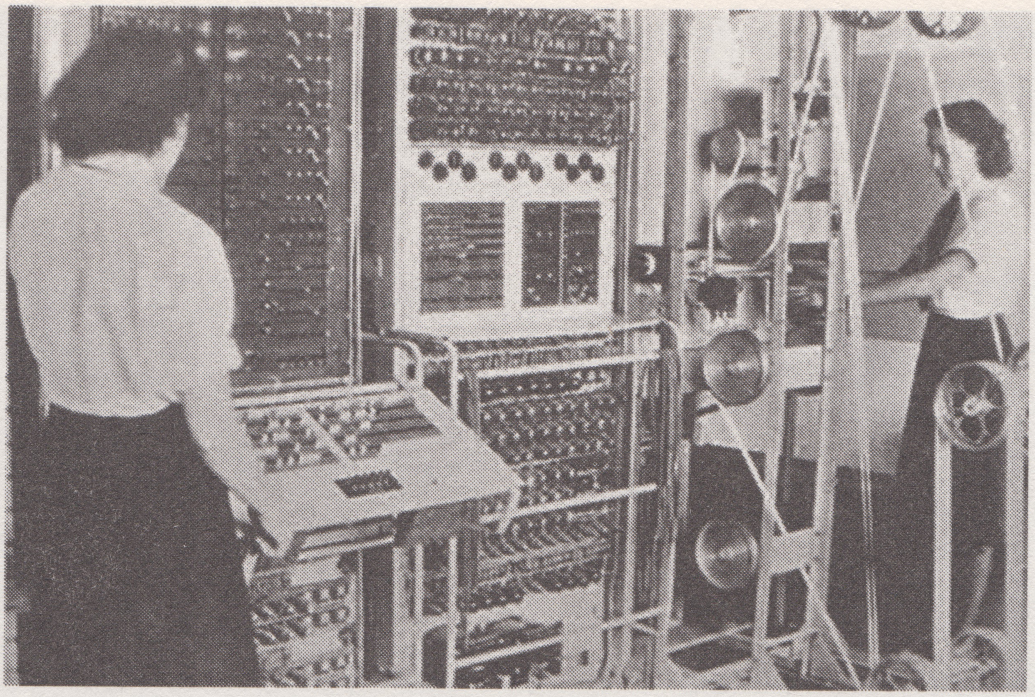
The theorem developed by Fisher is a good example of the importance played by mathematics in the development and subsequent progress of biology. It was in the 1930s when biological problems began to be expressed using mathematical notation. From this point onwards, the tendency to undertake quantitative research in biology has been unstoppable. Another important milestone in mathematical biology was the proposal formulated by Alfred J. Lotka in 1925, and by Vito Volterra the following year, for the model commonly referred to as the Volterra–Lotka predator–prey model. It is one of the most famous mathematical models in the discipline, and one of the most widely used in ecology. It will be explained in depth in Chapter 6.

The computer in the mathematical study of life

In the aftermath of World War II, and as a consequence of a conflict of this scale, the first computers appeared in Britain and the United States. The two countries, which were allies, had been competing to be the first to build a computer. The competition was not driven by scientific and commercial applications but by military requirements. The enemy that was to be fought was the Soviet Union, giving rise to a new geopolitical era known as the 'Cold War'. This new era affected the work of scientists throughout the world.

Although historians of science have regarded 1946 as the year in which the first computer was born in the United States, the popular ENIAC (Electronic Numerical Integrator And Computer), it is now known that Colossus, which was built in Britain in 1944, was in fact the pioneer of our current computers.

In 1950 Alan Turing, one of the greatest British scientists of the 20th century, built the ACE (Automatic Computing Engine) at the National Physical Laboratory outside London. It was a computer with a storage capacity similar to the early Macintosh computers in the 1980s. Turing's computer was the



Colossus, the first computer in history, built in the United Kingdom in 1944.

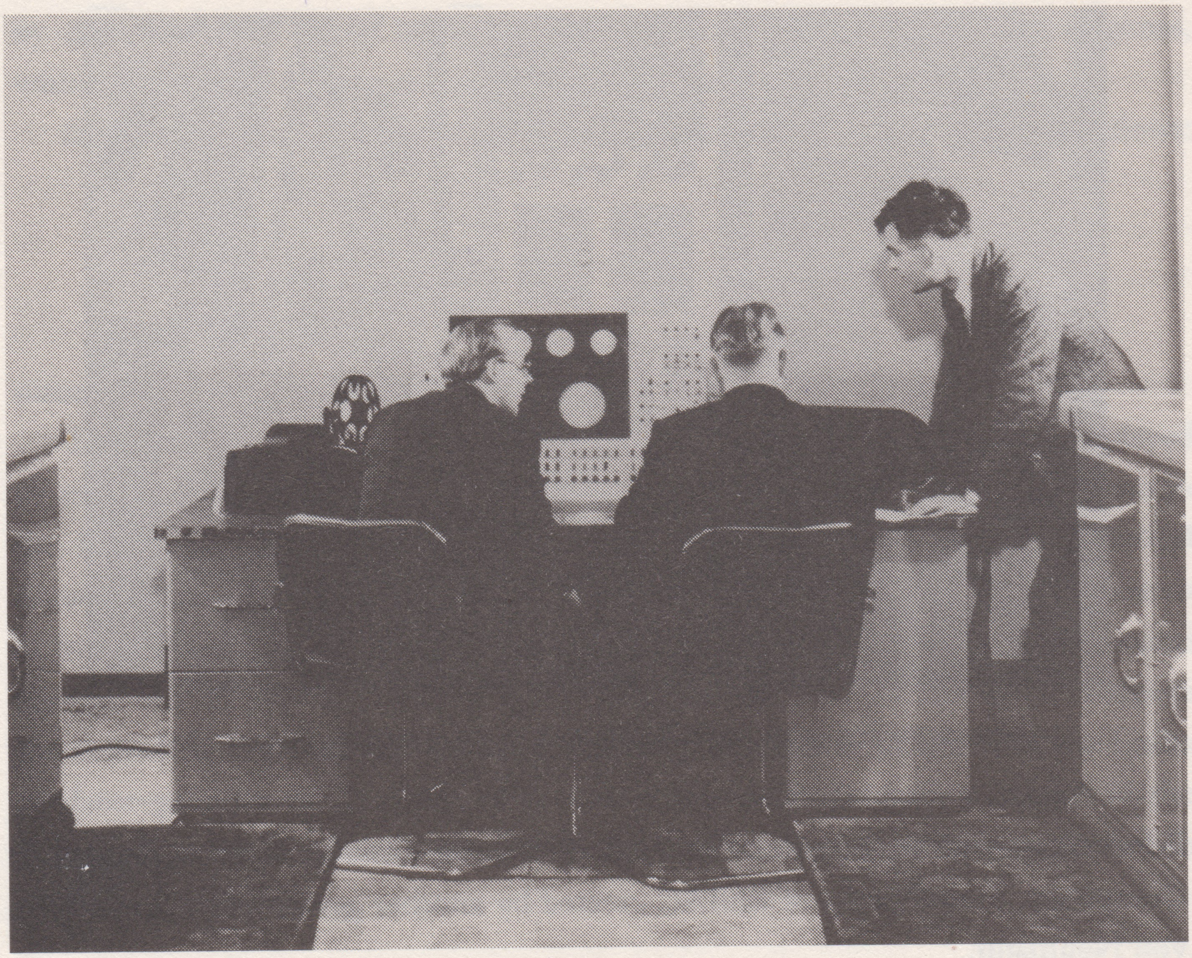
British answer to the American EDVAC (Electronic Discrete Variable Automatic Computer), the offspring of ENIAC created by another genius of the time, John von Neumann.

In order to 'defeat' their rival EDVAC, the British created EDSAC (Electronic Delay Storage Automatic Calculator), another computer with similar properties. However, at this point, the UNIVAC (UNIVersal Automatic Computer), was born in the United States, a direct descendant of ENIAC and EDVAC, making the company behind its construction – Remington Road – the first in the world to offer commercial computers.

The contributions of Alan Turing

In 1948, the University of Manchester had one of the most advanced computers of the time and, in 1951, it already had the Ferranti Mark I, a computer used by Turing for his work. From 1952 until his death in 1954, Turing was one of the first scientists to use computers to mathematically handle and simulate a problem from biology.

At the time, Turing was extremely interested in the mathematical study of morphogenesis. One of the most important problems in the discipline consists of explaining how living things acquire their final shape, such as how trees and other plants all subscribed to a particular shape, how the body form of arthropods was



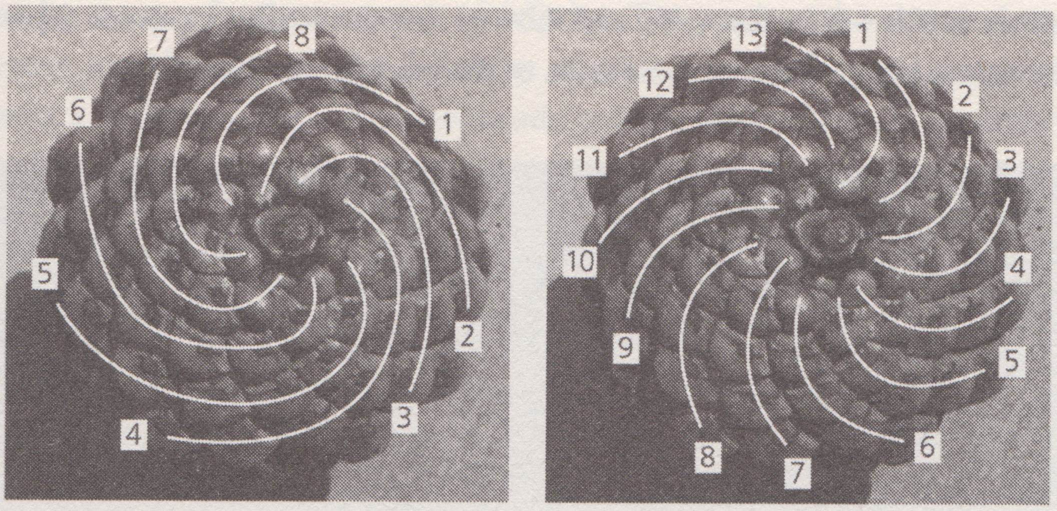
The Ferranti Mark I computer with Alan Turing (standing, to the right).

made of linked section and how worm bodies were built from round segments. Another of the classical problems studied in morphogenesis is the formation of patterns, such as those found on the skin of vertebrates, such as a zebra's stripes or the circular marks on dalmatians (the dogs, not the residents of the Adriatic coast).

Turing led the way with a new approach in the study of biological problems with the help of computers and was one of the pioneering researchers in the computational approach to biomathematics. In this way, Turing's studies promoted an applied approach to this discipline, bringing it close to the traditional laboratory work of biology. This led biologists and other scientists to dedicate themselves to the mathematical study of life throughout the 20th century and continuing to the present day. Turing also opened up a new field in mathematical biology by stating a mathematical theory of morphogenesis for the first time. In one of his studies, he applied the Fibonacci series to the structures of plants.

The Fibonacci series (0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, etc.) is obtained using the following procedure: 0 is assigned to the first term in the series, making a_1

$= 0$, and 1 to the second term a_2; the following terms of the series, a_n, are given by adding the two previous terms, such that $a_n = a_{n-1} + a_{n-2}$. Curiously, the number of petals and sepals on flowers, or the spiral arrangement of the scales of pine cones or the leaves of a plant conform to this series.



The number of spirals (8, 13) in each direction of the pine cone are contiguous terms from the Fibonacci series.

The presence of Fibonacci numbers in plants was referred to by Fibonacci as phyllotaxis. In the case of the leaves of plants, their arrangement according to this series optimises their exposure to sunlight. A leaf competes with other neighbouring leaves to capture the available light. What then is the best layout to ensure all leaves capture the maximum possible amount of sunlight? The Fibonacci series appears to provide a good solution.

Pursuing his research, Turing made his most famous contribution in this area, the mathematical model of reaction-diffusion. The researcher expressed his ideas in an article entitled *The Chemical Basis of Morphogenesis*, published in 1952 in the prestigious scientific journal of the Royal Society. Turing attempted to use differential equations to explain a phenomenon that was of genuine interest to him, in spite of the fact that his background was in mathematics and not biology. Regardless, Turing asked how it was possible that a pattern of stripes or marks could emerge from a homogeneous tissue of cells in a highly similar embryonic state, such as vertebrates' skin cells. From a biological point of view, the resulting pattern is the consequence of the differentiation of different types of cells, specifically pigmented cells and nonpigmented ones. Consequently, the skin of a zebra, for example, would be the result of the 'rupture' of the initial uniformity of the embryonic skin cells.

However, of greatest interest to Turing was the biological mechanism that contained such patterns, since this assumed that the resulting pattern of cells (in this case a zebra's stripes) represented an unstable state. For Turing, the stable state would be the uniform state of the embryonic skin that had yet to adopt a characteristic pattern. Using the Ferranti Mark I, Turing carried out simulation experiments, using the computer as if it were a test-tube, and showed that the resulting pattern depended on the values assigned to the parameters of the mathematical model.

The stripes of the zebra's skin are an example of Turing's reaction–diffusion equations.

In a mathematical model, a parameter is a value that represents a quality of a certain phenomenon that is not directly observable. Turing obtained certain patterns that were extremely similar to the distribution of the tentacles of a hydra and others that suggested the arrangement of flower petals. Assuming cells were circular, Turing also modelled the blastula. This is one of the early states through which an embryo passes, in which it is possible to observe the beginning of the formation of patterns. He studied the embryos of amphibians and hedgehogs, subjects that are currently widely used as models for morphogenic studies due to their properties.

Turing's hypothesis proposed that the formulation of patterns took place by means of reaction–diffusion processes. According to this conjecture, in an embryonic tissue, in a group of aggregate cells on a plane there would be pigmented cells that produce a class of substances referred to as morphogens. The molecules of this mysterious substance react with each other once they have extended throughout the embryonic tissue by means of a phenomenon of diffusion. The result of the chemical reaction between morphogens was the definition of what is referred to as a concentration pattern, a 'footprint' that will subsequently provide information to the embryonic cells about the final pattern by which they must distinguish themselves. Hence, the 'drawing' of stripes, marks or any other phenomenon that we can observe on an animal will be nothing more than a replica of the concentration pattern. Although they will not be analysed in detail here, these are the famous reaction-diffusion equations proposed by Turing:

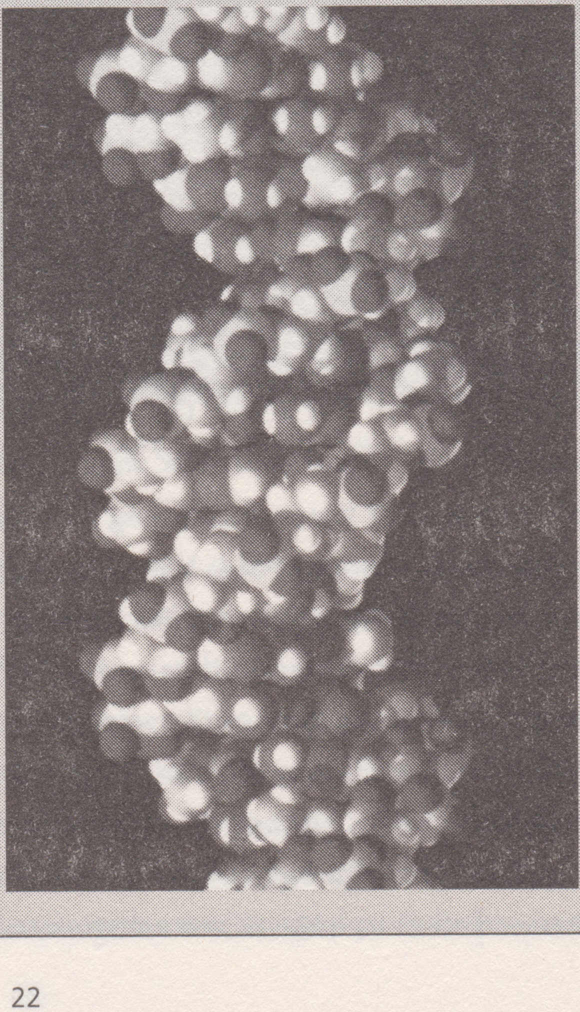
$$\frac{\partial M_A}{\partial t} = f(M_A, M_I) + D_A \nabla^2 M_A,$$
$$\frac{\partial M_I}{\partial t} = g(M_A, M_I) + D_I \nabla^2 M_I.$$

These expressions explain how the quantity or concentration of two substances conjectured by Turing vary over time; these he called the activator morphogen (M_A) and the inhibitor morphogen (M_I). These substances are only produced or synthesised by pigmented cells, as we have mentioned. For their part, $f(M_A, M_I)$ and $g(M_A, M_I)$ are two functions that represent the reaction between them, and the expressions $D_A \nabla^2 M_A$ and $D_I \nabla^2 M_I$ refer to how the two classes of morphogens extend or spread out across the tissue. Hence, once the morphogens have been released by the pigmented cells, their diffusion will be similar to that of a lump of sugar in a glass of water. According to Turing, the activator morphogen stimulates its own production as well as that of the inhibitor. Another peculiar property is that the inhibitor morphogen reaches a greater distance of diffusion than the activator morphogen; their different distances of diffusion are represented by D_A and D_I, the respective diffusion rates of the activator and inhibitor morphogens.

In 1954, Alan Turing took his life at the young age of 41, an event that constituted the disappearance of one of the most brilliant scientists of the 20th century. Proof of his genius lies in the fact that the chemical substances he predicted mathematically, the so-called morphogens, were discovered experimentally many years later, at the start of the 1990s. Furthermore, some of the patterns studied by Turing with his Ferranti Mark I were discovered in the Koran angelfish, or *Pomacanthus semicirculatus*. At present, morphogenesis is one of the fields of study in mathematical biology, and scientists such as Murray and Meinhardt have been witness to the fascinating path on which Alan Turing set out many years ago.

LIFE IS INFORMATION

One year before the death of Turing, in 1953 Watson and Crick proposed the double helical structure of DNA. Prior to this, scientists such as John von Neumann and Alan Turing were already making the claim that "life is information". However, this vision, which has now been fully accepted, was revolutionary at the time. The representation of the DNA sequence – the material that makes up genes – uses four letters that correspond to the four possible subunits of which DNA is composed: *A* for adenine, *T* for thymine, *G* for guanine and *C* for cytosine. In parallel to this, another important development of the period was informatics. Computers handle a representation of information in binary notation, coded into sequences of just two digits, zero and one. Consequently, the computer is a machine with a natural potential for studying life, describing its parts, exploring its most intimate mechanisms and making predictions about its future. From then on, the computer has become an instrument that has helped consolidate a close relationship between mathematics and biology. With the passing of time, the computational approach initiated by Turing not only contributed to this consolidation, attracting the attention of numerous scientists, but also led to both disciplines merging into one – mathematical biology.

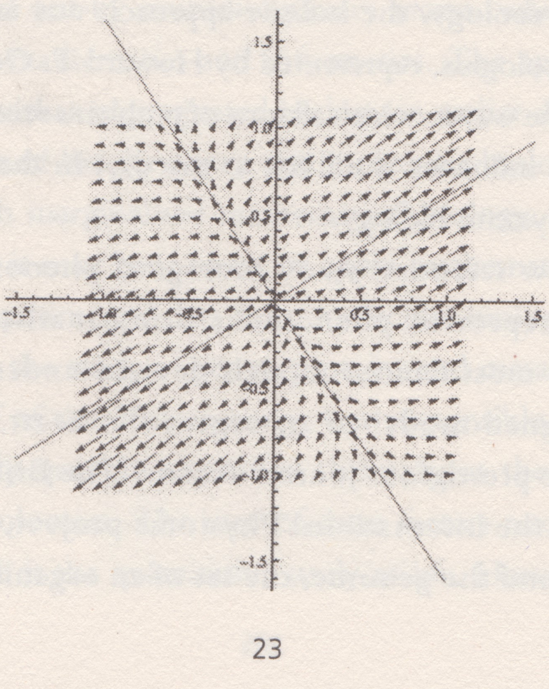


The DNA molecule as described in 1953 by Watson and Crick.

The dawn of systems biology

From the 1950s and 1960s, the mathematical study of living things – and life in general – using computers was carried out assuming that plants, animals and microorganisms were in what was referred to as a 'steady state'. It was also assumed that living things were in a steady state thanks to mechanisms for self-regulation. However, in return for remaining in a steady state, living things were required to expend a considerable amount of energy through these self-regulation mechanisms or homeostasis. The importance of homeostasis had already attracted the attention of pioneering researchers such as the British scientist W. Ross Ashby in the 1940s. For example, people have a natural tendency to have a certain level of glucose in their blood. When faced with excess glucose, the pancreas releases insulin to convert it into a glycogen store, whereas if there is a deficiency it releases glucagon which breaks the glycogen into glucose. In other words, the body must 'work' to ensure nothing changes.

Another common way of tackling the mathematical study of life with the help of computers, insofar as is possible, assumes a phenomenon exhibits 'linear behaviour'. Linear systems are the easiest to study, since the overall state or behaviour of a system is – mathematically speaking – the sum of its parts. For example, let us consider a primitive being z, whose physiology is so simple as to be made up of just two organs, x and y. If we represent the physiological states of x and y as $f(x)$ and $f(y)$, the vital state of the organism $f(z)$ will be the sum of the states of its organs $f(x) + f(y)$. In the steady state, the derivative of $f(z)$ will be 0; in other words, the mathematical function that describes its vital state will have stopped growing or decreasing.



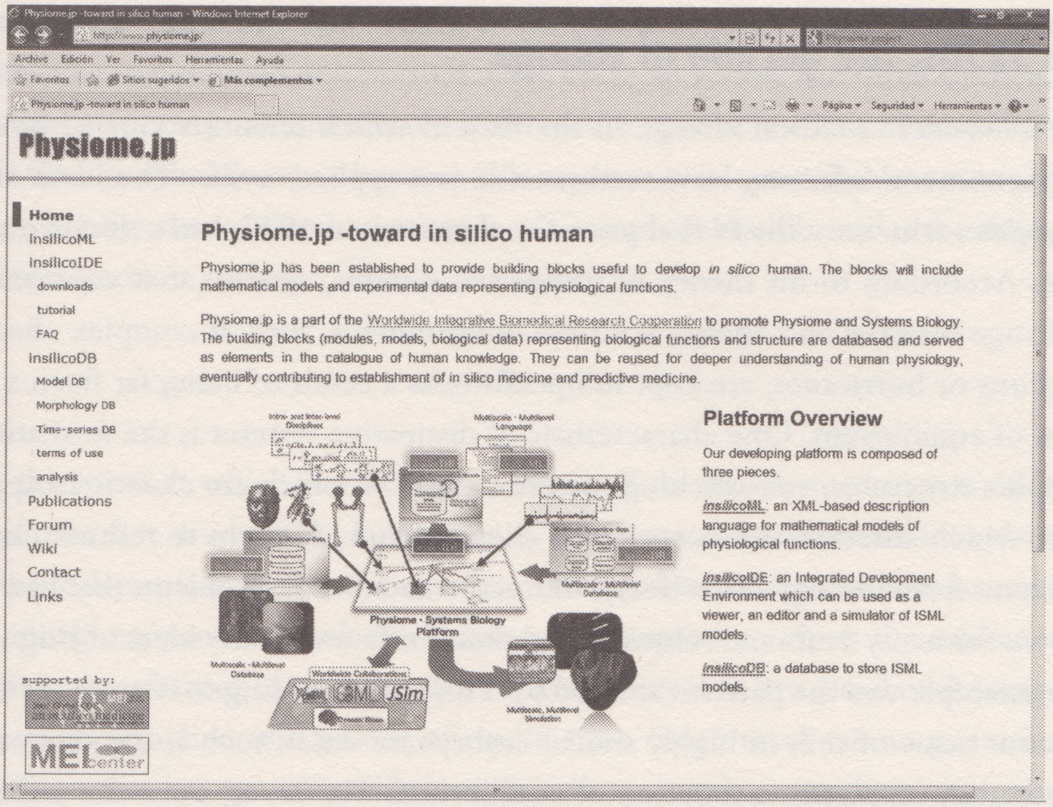
Linear systems – the most accessible to study from a mathematical point of view.

The mathematical study of linear systems is related to von Bertalanffy's holistic organicist approach. This approach did not only impact biology but also affected other disciplines by means of a work published in 1968, originally titled *General System Theory: Foundations, Development, Applications*. In fact, this theory had a considerable effect on the way in which scientists use computers to simulate phenomena as diverse as the climate, metabolism, sales and financial markets using a mathematical model. A system is a set of objects with a physical existence, such as parts or elements, or of an abstract nature, such as variables with attributes and properties, but most importantly they all have connections and relationships between them.

One important aspect of von Bertalanffy's systems theory is that the systems are immersed in an environment. This means that there are not only interactions between the parts of a system, but since the systems are open these parts also interact with the environment. The interaction between a system and the environment takes place through the entry of information originating from the system's environment, or input, which gives rise to a response towards the environment, known as the output, once it has been processed or transformed by the system. Concepts such as self-regulation or feedback, and the notion of balance or homeostasis, arise spontaneously as part of this approach.

This global view of nature, which regards a system as a 'whole' is referred to as holistic, and it exerted a huge influence on how we see the world throughout the 20th century. This influence is not only apparent in biology, but also in sociology, economics and even our understanding in disciplines as diverse as chemistry and linguistics. Furthermore, it has also influenced the way in which mathematics is applied to the real world. In ecology, the holistic approach was introduced by a North American school of ecologists, represented by Howard T. Odum. In the 1950s, his vision revolutionised the way in which all sorts of problems related to the environment were studied – and its influence is still felt to this day. In the 1960s, this resulted in what is referred to as systems biology.

This approach saw scientists study biological phenomena from a holistic point of view and represent phenomena using mathematical models. For example, one of the most famous models devised under this approach is the first computer-designed model of an organ, the heart, published by Denis Noble in 1960 in the prestigious journal *Nature*. The British researcher played an important role in the international Physiome project, which began in 1990 and seeks to understand the genome, the set of an organism's genes. However, this understanding is arrived at by carrying out computer simulations using mathematical models of physiology.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Multiscale · Multilevel Database
Worldwide Collaborations
JSim
Multiscale, Multilevel Simulation

Physiome.jp -toward in silico human

Physiome.jp has been established to provide building blocks useful to develop *in silico* human. The blocks will include mathematical models and experimental data representing physiological functions.

Physiome.jp is a part of the Worldwide Integrative Biomedical Research Cooperation to promote Physiome and Systems Biology. The building blocks (modules, models, biological data) representing biological functions and structure are databased and served as elements in the catalogue of human knowledge. They can be reused for deeper understanding of human physiology, eventually contributing to establishment of in silico medicine and predictive medicine.

Platform Overview

Our developing platform is composed of three pieces.

insilicoML: an XML-based description language for mathematical models of physiological functions.

insilicoIDE: an Integrated Development Environment which can be used as a viewer, an editor and a simulator of ISML models.

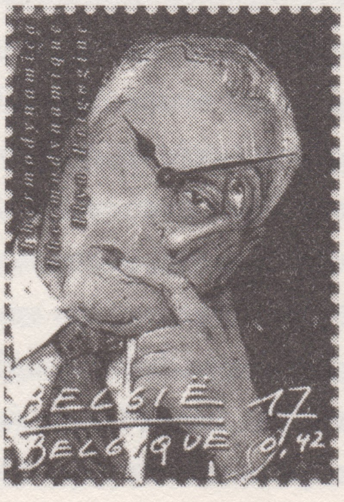
insilicoDB: a database to store ISML models.

Web page from one of the various institutions linked to Physiome, a systems biology project.

One feature of the project is the integration of various biochemical levels, from or cells, all the way to organs. In fact, an important property of systems biology is that projects are carried out by multidisciplinary teams, which include members from biology, physics, mathematics and informatics. The approach is in contrast to the reductionist view that impregnated biology in earlier decades and sought to explain all life in terms of biochemistry and molecular biology. For a while, the success of this approach marginalised mathematical biology, and any attempt, no matter how interesting it may have been, to apply mathematics to life. However, the accumulation of experimental data from molecular biology, in addition to the spectacular advances in the study of genes, proteins and metabolism that occurred during the second half of the 20th century, was responsible for the rise of three disciplines whose study quickly expanded throughout the world – genomics, proteomics and metabolomics. The sum of these factors rescued systems biology from oblivion, and with it the quantitative study of life. However, it was not until the end of the 20th century that systems biology became fashionable once again, and helped to resurrect, albeit indirectly, an interest in mathematical biology.

The 1970s: the decade of change

The 1970s saw a radical change in the way in which scientists viewed biological phenomena, affecting how mathematics was applied to life. The ideas of Ilya Prigogine, who won the Nobel prize for chemistry in 1977, had a decisive influence. According to his theory of dissipative systems, systems that continuously exchange material and energy with the environment, such as complex chemical reactions or hurricanes, are kept in operation as a result of being far from a situation of equilibrium. One characteristic of dissipative systems is the formation of complex structures, eye-catching patterns, some of which are chaotic in appearance, which attracted the attention of scientists and led them to rethink classical problems from biology. Effectively, biomathematics took problems that had been known for many years and reinterpreted them in line with the ideas of Prigogine. One example was the patterns studied by Turing. According to Turing, a homogeneous tissue of cells in highly similar embryonic states, such as the skin cells of vertebrates, represents a situation of equilibrium. However, once the cells have differentiated themselves, the animal will exhibit a pattern of stripes or marks on their skin. For Turing and Prigogine, the maintenance of this pattern by the animal throughout its life represented a situation that was far from equilibrium. The reaction–diffusion equations are one of the formal tools used by biomathematicians to study certain dissipative systems, such as the patterns of marks on the skin of certain vertebrates, as we have mentioned.



Artistic Belgian stamp in honour of Ilya Prigogine (1917–2003), issued two years before the death of the eminent Russian scientist.

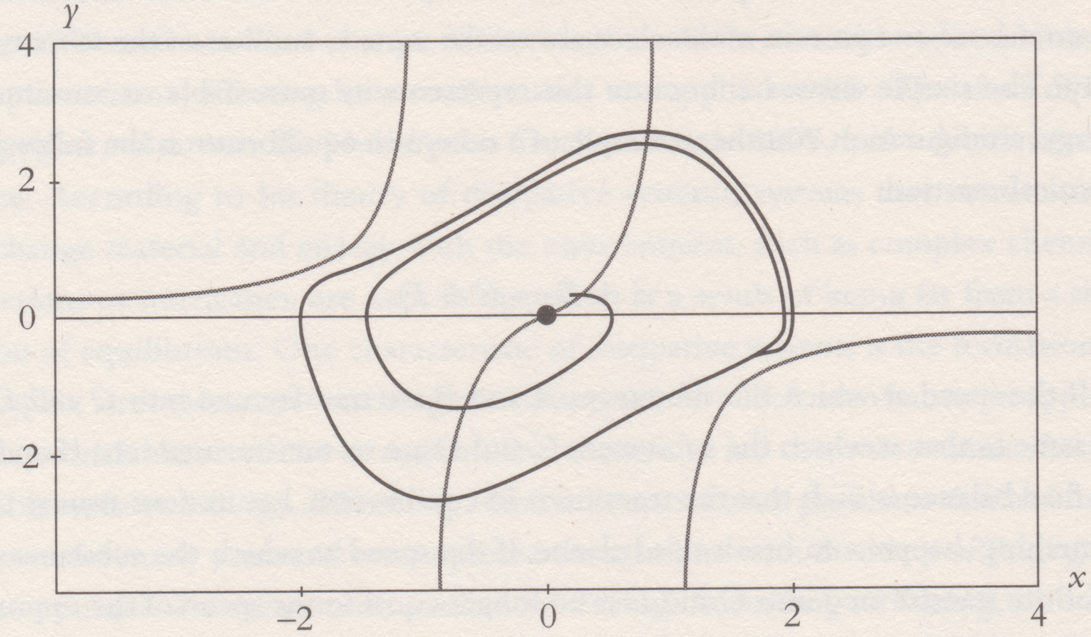
Another characteristic of systems that are out of equilibrium is their oscillation, one example being the famous Volterra–Lotka predator–prey equations. However, there are unfortunately no universal principles governing the formation of patterns as attractive as those that can be seen in dissipative systems, while it is the case for systems that maintain an equilibrium. One example is how the three-dimensional appearance of one protein molecule is always the same as another of the same type. Why? The simple answer is because this represents its most stable or 'minimum energy' configuration. Another example of a system in equilibrium is the following chemical reaction:

$$A + B \rightarrow C + D.$$

If the speed at which the substances A and B are transformed into C and D is the same as that at which the substances C and D are re-transformed into A and B, the final balance is such that the reaction is in equilibrium. Let us now assume that 'something' happens to break this balance. If the speed at which the substances A and B are transformed into C and D is no longer equal to the speed of the opposite reaction, the reaction will be out of equilibrium. Since there are no general rules for systems that are out of equilibrium, there is no common mathematical method for their study, meaning that scientists must carry out experiments using computer simulations. When it comes to life, there are numerous examples of systems that are out of equilibrium. These ideas gradually served to form our modern vision of biology and hence its mathematical formulation.

The biology of modern mathematics

The study of systems that were out of equilibrium during the 1970s and the search for computational methods that permitted their simulation led to the study of nonlinear systems becoming popular in the 1980s and 1990s. In such systems, the behaviour of the system as a whole cannot be described as the sum of the behaviours of its parts. This is due to the existence of interactions between the parts. Let us return to the example of the primitive living organism, which we shall call z, and assume it is made up of just two organs, x and y. In the event that its physiological behaviour was nonlinear, the vital state of the organism $f(z)$ would thus be the product or multiplication, for example, and no longer given by the simple addition of the states of its organs $f(x)$ and $f(y)$. An example from everyday life is taking medicines. Taking two or more medicines does not imply the sum of their therapeutic effects, in fact quite the contrary, and there are many situations in which the interactions between medicines cause the opposite effects of those intended, and can actually cause illness.



Nonlinear systems are difficult to study and there is no mathematical method common to all systems, even though they may exhibit similar behaviour. Consider, for example, a pendulum. After being pushed it will oscillate until it comes to rest. Similar situations occur in the immune system and long-term memory.

One peculiarity of nonlinear systems is the possibility of chaotic behaviour. Chaotic systems are systems whose behaviour is complex and difficult to predict, since they are both attracted and repelled from a situation of equilibrium at the same time. Examples of systems that exhibit such behaviour include the atmosphere and climate, tectonic plates, epilepsy and populations that behave in line with the so-called Verhulst equation, as well as many other situations that we will describe in this book. The study of chaos was responsible for the popularity of fractals in biology, with examples from the natural world including phenomena as typical as the branching system of plants.

In the second half of the 1980s, scientists brought the study of nonlinear, chaotic and dissipative systems together under the common name of 'complex systems'. Biology is one of the most widely studied disciplines in this class of systems, which occur, for example, in ant colonies, the brain, the immune system, the cell, morphogenesis and ecosystems. In many cases they are studied using standard methods from mathematical biology. However, there are other cases in which the complexity of the system is such that it requires the use of alternative methods to get approximate solutions using computers. These techniques are referred to as heuristic methods. For example, at present the cell automaton technique represents a serious alternative for modelling and simulating complex systems for which differential equations are not known. Ant colonies constitute a classic example of cellular automata. In other cases, although the differential equations are known, such as in the case of the skin patterns in vertebrates studied by Turing, it is more feasible and quicker to simulate them using cellular automata. Furthermore, cellular automata make it possible to draw patterns, such as the stripes of a zebra, something that is not possible with differential equations. Another example of this latter situation is Wa-Tor, a cellular automaton based on the Volterra–Lotka predator–prey model.

Since the 1980s, one of the events that has helped to stimulate interest in mathematical biology has been the widespread adoption of scientific software in mathematics, especially when it comes to symbolic computation. These are computer programs that make it possible to find the solution to a problem when it takes the form of an expression and not a numerical value. For example, the calculation of a definite integral such as

$$\int_0^2 x^2\,dx$$

is relatively easy, and gives us a numeric value if we use a computer. To solve the example using a computer, all we need to do is apply classical numeric methods, such as Simpson's rule, the trapezoidal rule, etc. However, how can the integral shown below be calculated?

$$\int e^x \cos x\,dx.$$

Thanks to symbolic computation programmes it is possible to find this integral quicker with a computer than by hand. This type of software has introduced biologists and other life scientists to the handling of sophisticated mathematical methods, greatly facilitating the resolution of problems in mathematical biology.

In this chapter, we have provided a sketch of the main historical developments of the discipline. Note that not just the origins, but also the subsequent development and current consolidation of mathematical biology is strongly influenced by the interpretation of the physics of life and organisms for each historical period.

Furthermore, mathematical biology is a discipline that has promoted the minute analysis of biological phenomena and experimental data. At present, the design of mathematical models in biology, used to carry out sophisticated computer simulation experiments, represents another important contribution made by the discipline.

The mathematical model in biology

Human beings have always felt the need to understand, manipulate and predict the behaviour of all that is present in nature. Scientists from all periods and places have inherited this need, constructing models of the world that surrounds them. Generally speaking, a model is a representation or abstraction of a system or certain phenomena present in the real world.

A model may have multiple uses. On the one hand, it makes it possible to understand certain phenomena, explaining them by means of their description, such as a model of the cellular cycle or the metabolism of glucose. On the other, and this is especially important, it makes it possible to predict the state or future behaviour of a system or phenomenon that is being studied, such as climatological predictions, or analyse particular hypothetical situations, such as the effects of an accident at a nuclear power plant on the fauna and plant life in the affected region.

Furthermore, there are models that can be used by scientists to prove certain conjectures or hypotheses by carrying out computer simulation experiments. For example, it is possible to carry out simulation experiments to test a hypothesis on the origins of life, or a mechanism to explain the evolution of a species. In other instances, a model can be used to inspire, for example, a group of engineers in their search for a certain solution to a given problem. Regardless, the construction of models is one of the essential tasks of science, be it on account of their practical use or because it is the only way to build our vision of how the world and the Universe works.

In biology, just like in other disciplines, mathematical models are useful for creating an abstract representation of a system or phenomenon using mathematical language and its formalisms. For example, a model of a cell, the heart or an ecosystem represents its parts or subsystems and their interactions using mathematical expressions. These will relate a set of input variables, $I_1, I_2..., I_n$, or inputs to an output variable O. The input variables will represent quantities that can be observed by the scientist, and hence counted or measured. One of these input variables is often the time *t*, representing the moment at which the input values $I_1(t)$, $I_2(t)$..., $I_n(t)$ were obtained. Once these values have been determined experimentally or using any other procedure, such as by assuming certain theoretical assumptions, they are 'introduced' into the model. The mathematical expressions of the model then allow scientists to obtain the value of an output variable $O(t)$. This final value represents a property of the system, perhaps the one of greatest importance to the scientist since it is the object of their study. It is common for this quality to be the state or behaviour of the system or phenomenon at a certain moment of time *t*.

Mathematical expressions also contain parameters. In contrast to input and output variables, these represent qualities that cannot be directly observed by the scientist, such as the birth rate, the decay constant of an isotope, the reaction speed for a biochemical reaction, etc. Hence, their values are estimated in the field or in the laboratory.

To 'estimate' means that we make do with obtaining an approximate value of the parameter, making use of sophisticated statistical methods. However, there are occasions on which the value of the parameters is known beforehand, perhaps by consulting tables published by other researchers. One example of this is looking up the calories of various foods in a model dealing with diets. Other examples of 'known' parameters include the rate of infection of seasonal flu, or the generation time for a bacterial culture. However, what is the role played by such parameters? Their purpose is to link and relate the input variables $I_1(t)$, $I_2(t)$..., $I_n(t)$ to the output variable $O(t)$ by means of the expressions of the mathematical model.

Mathematical model with input variables (I) *and output variable* (O).

The computer: a test tube

Simulation is a fundamental concept related to the idea of mathematical modelling. A simulation experiment consists of predicting the future state of a system, or rather $O(t + 1)$, based on a computational model of the system being simulated. For example, the prediction of the weather for the coming days is based on a computational model of the climate; the prediction of the number of wolves and rabbits in a certain place is established by means of a computational model of the predator–prey relationship; and the number of people affected by seasonal flu on successive days can be predicted by using a computational model of an epidemic for this purpose. These are just some examples that illustrate the usefulness of simulation when it comes to predicting the future states of a system. Hence, prediction requires a computational model.

Generally speaking, a computational model is a computer program that has been written in a programming language (Visual Basic, C/C + +, Java, etc.) to implement a mathematical model. Hence, a simulation experiment consists of 'putting to work' a mathematical model on a computer to find the answer to questions related to the future of a certain phenomenon or system – it asks "What happens if...?" Hence, the computer becomes a test tube, a genuine laboratory for investigating matters that cannot be directly tackled in real life.

The procedure for carrying out a simulation experiment is simple, and there are various possibilities. In first place, a simulation experiment may consist of defining the initial conditions and asking what the future state of the system will be. The initial conditions are the values of the input variables for the model, which are known and are used for the forecasting.

Scientists refer to this starting point as 'time zero', and hence the initial conditions are written as $I_1(0)$, $I_2(0)\ldots$, $I_n(0)$. For example, if there are currently 1,247 people affected by swine flu, 1,240 of which have survived and seven of which have died, the initial conditions will be

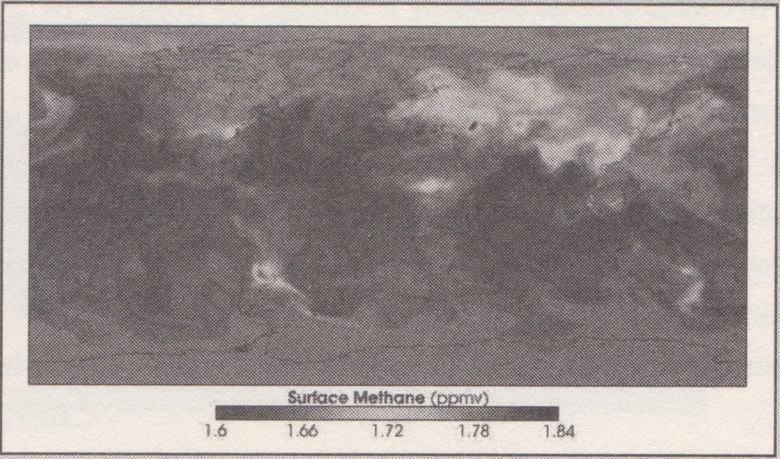
$$I_1(0) = 1{,}247,\ I_2(0) = 1{,}240 \text{ and } I_3(0) = 7.$$

Based on this initial situation, and using a computational model of the epidemic, we can pose the question: how many people will be affected within seven days.

The second type of simulation experiment may consist of altering the value of the parameters and asking how these values affect the future state of the system. For example, in the swine flu example, what happens if instead of using a mortality rate of 0.78%, a rate of 2.96% is used? How many people will die within a month?

COMPARING MODELS

There are situations in which a simulation experiment may consist of predicting a phenomenon and comparing the predictions obtained using different computational models based on different mathematical models. This is because there are various mathematical models for dealing with a given phenomenon. For example, it is possible to compare various mathematical models of the climate based on their different predictions for a common situation, simulate the behaviour of an ant colony with different computational models, or compare the number of predators and prey over a given time interval using a cellular automata model with the values obtained using the Volterra–Lotka equations.

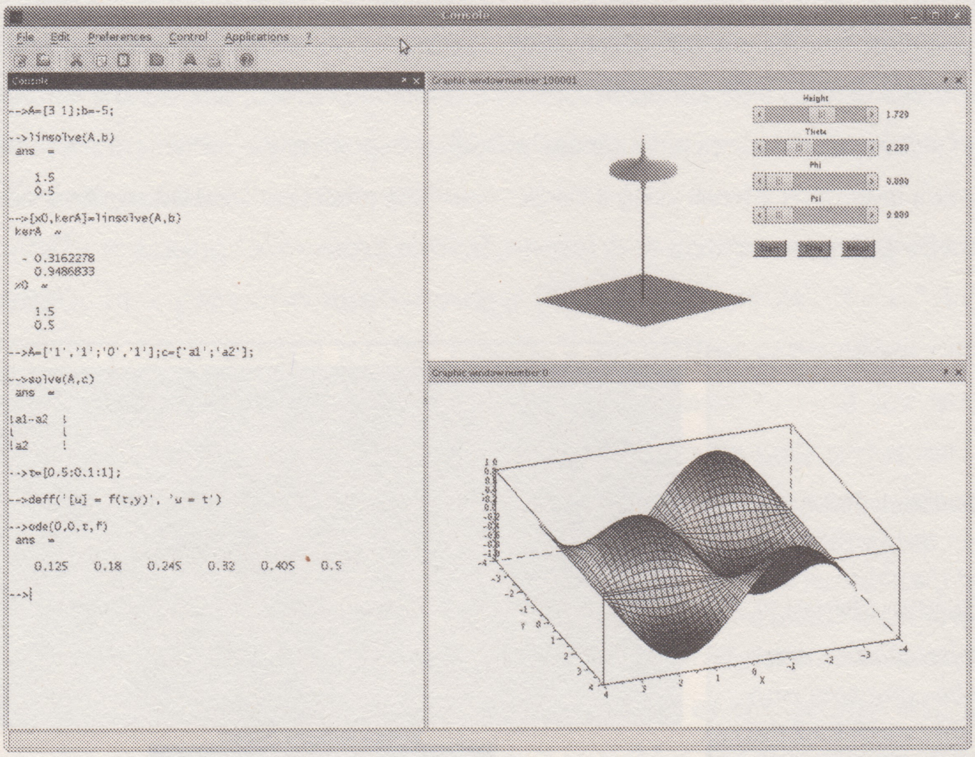


The increase of methane in the Earth's crust and the stratosphere, as determined using a computational model, can be compared with other models of the same phenomenon.

Finally, a third type of simulation experiment may involve determining the future state of a system given a set of initial conditions and the values of specific parameters.

Symbolic computation software

The first programs of this nature appeared in the 1960s, representing one of the first commercial artificial intelligence products. They were first used by physicists, although with the passing of time they were also adopted by other specialists. In the early days of symbolic computation, programs such as Schoonschip and MathLab were developed. However, it was not until the appearance of muMath, Reduce, Macsyma and Derive that symbolic computation software became popular in academic circles. At present, in addition to being used in universities and educational institutions, it is also a standard tool for scientific and engineering projects. Today the most popular commercial programmes are Maple and Mathematica, although there are also free software programmes such as SciLab and Octave.



```
-->A=[3 1];b=-5;

-->linsolve(A,b)
 ans  =

    1.5
    0.5

-->[x0,kerA]=linsolve(A,b)
 kerA  =

  - 0.3162278
    0.9486833
 x0  =

    1.5
    0.5

-->A=['1','1';'0','1'];c=['a1';'a2'];

-->solve(A,c)
 ans  =

!a1-a2  !
!       !
!a2     !

-->t=[0.5:0.1:1];

-->deff('[u] = f(t,y)', 'u = t')

-->ode(0,0,t,f)
 ans  =

    0.125    0.18    0.245    0.32    0.405    0.5

-->
```

Screenshot of SciLab, a free scientific calculation and symbolic computation program.

Nowadays, these programs represent an irreplaceable tool in mathematical biology and are essential when it comes to studying so-called dynamic systems in ecology, epidemiology, pharmacology, etc.

Let us consider some examples of simple operations that illustrate their use. Imagine that in a study of the flora of a certain region, we are required to find the derivative of the following expression:

$$\frac{d}{dx}(x^3 + \sin(x)),$$

where x is a variable related to plant cover.

We can use a symbolic computation programme to calculate the derivative. In our example, we'll use Derive 4.11 (for Windows). Using the symbolic notation for this environment, the expression is represented as: DIF(x^3 + SIN(x), x), and its derivative is $\cos(x) + 3x^2$.

Another useful example involves calculating the limits of a function. For example, given the expression:

$$\lim_{x\to 2}\frac{x^5-2x^3}{4x^2-6},$$

which, without going into details, is symbolically represented as: LIM((x^5 − 2 · x^3)/(4 · x^2 − 6), x, 2, 1), we find that the limit is 8/5.

These examples illustrate some simple problems in which symbolic computation environments can be used. In addition to making it possible to edit and correct expressions, they also open up many other possibilities, such as representing graphs in two or three dimensions, linking to external programs and making use of libraries of routines developed for the most wide-ranging computational chemistry applications. They also have functions for evolutionary computation, bioinformatics, statistical techniques, differential equations and many more applications. The tasks they are used for include simplifying expressions, obtaining Taylor polynomials, factorising polynomials, calculating limits, derivatives and integrals, and operations involving matrices and vectors.

The inclusion of a programming language means that the user can write programs with their own 'procedures' for calculations. Their application to a certain class of problems from biology has led to a new specialism in mathematical biology, algebraic biology. The discipline arose in 2005 as a result of the application of symbolic computation methods in biology. It is used to build models that can provide satisfactory explanations of biological phenomena, and places the emphasis on the 'biological problem' as opposed to the mathematical manipulation of symbolic expressions. At present it is regarded as a branch of systems biology. Its applications include the analysis and modelling of biological systems using algebraic methods from symbolic computation, and it can be used to design models for biochemical reactions, gene regulation, cellular biology and various problems from molecular biology.

However, its applications go beyond the modelling of cells and molecules, and it is also useful when it comes to studying populations of organisms, epidemiology, etc. In fact, there are applications as sophisticated as the construction of phylogenetic diagrams, or 'trees of life', showing the evolutionary relationships between various species. There is even, without going into too much detail, a model for one of the most famous mechanisms from molecular biology, the *lac* operon of the bacteria *Escherichia coli* (better known as *E. coli*). This system was discovered by Jacob and Monod, who were awarded the Nobel prize for medicine in 1965. Yet, how useful can we expect a recently developed computational model of something discovered in the 1960s to be? In fact, in addition to being new, computational algebra constitutes a powerful tool for systematically analysing and building biological models. It is not just a case of new discoveries in the laboratory, but of a procedure that allows researchers to better understand, manipulate and even 'play' with all the elements involved in a complex mechanism such as the *lac* operon.

Some examples of the application of mathematics to biology

The final section of this chapter will discuss four important cases of the application of mathematics to biology – the Leslie matrix, cellular automata, the predator–prey model using cellular automata, and set theory in a mathematical model of the immune system.

Managing populations of deer, squirrels and other forest animals: the Leslie matrix

The ecologist Patrick H. Leslie was born in 1900 and worked as a member of the Bureau of Animal Population in Oxfordshire. In 1945 he published a model of population structure that has been widely used in the ecology of populations and demographics. The model makes it possible to determine the growth of a population, given the structure of its age. Leslie combined two functions, one related to fertility and the other related to mortality, devising a population matrix named after him: the Leslie matrix. The Leslie matrix is square, or rather it has the same number of rows and columns, with the number coinciding with the number of elements in a given vector. Furthermore, the model assumes that the population is completely isolated, without the addition or loss of individuals as the result of migration. Another limitation is that only females are studied and counted, since the model only applies to animals that employ sexual reproduction and, in general, the number of males does not affect the growth of a population. The vector we referred to above represents the number of individuals belonging to a specific age group.

Let us explain Leslie's model using the following example. We'll assume that in a natural environment, such as a park or reservation, a sample of deer is taken that counts the number of female individuals at time *t* which belong to the age groups 0, 1, 2, 3 and 4: N_t^0, N_t^1, N_t^2, N_t^3 and N_t^4. Note that 0, 1, 2, 3 and 4 are just labels that denote age intervals, for example, in years, ordered from the youngest to the oldest. In our example, it is assumed that the life expectancy of deer can be grouped into five classes or age groups. Furthermore, it is also assumed that their fertility is known. This means that ecologists who work in the reserve know the average number of offspring for a female of a given age. If we consider the population as a whole, the number of newly born deer added to an age group made up of the youngest individuals is the same for the following generation, or rather at time $t + 1$:

$$N_{t+1}^0 = f_0 \cdot N_t^0 + f_1 \cdot N_t^1 + f_2 \cdot N_t^2 + f_3 \cdot N_t^3 + f_4 \cdot N_t^4.$$

We now take the next step in our argument. Note that, from time to time, a deer will die, regardless of its age. Under these circumstances, the individual will not survive to progress beyond its current age group. Let s_0, s_1, s_2 and s_3 be the fraction or percentage of individuals that survive for a given age group, and hence progress to the following group. This number is expressed as a value between zero and one (i.e. the probability). For the purposes of the model, this means that the number of female deer that progress from one age group to the next is given by, $N_{t+1}^1 = s_0 N_t^0$, $N_{t+1}^2 = s_1 N_t^1$, $N_{t+1}^3 = s_2 N_t^2$ and $N_{t+1}^4 = s_3 N_t^3$. In mathematical biology. The Leslie model is a mathematical model that illustrates the dynamics of the population with great elegance. Leslie brought these expressions together in a transition matrix *L*:

$$\begin{pmatrix} f_0 & f_1 & f_2 & f_3 & f_4 \\ s_0 & 0 & 0 & 0 & 0 \\ 0 & s_1 & 0 & 0 & 0 \\ 0 & 0 & s_2 & 0 & 0 \\ 0 & 0 & 0 & s_3 & 0 \end{pmatrix}$$

Finally, let us use a vector N_t for generation *t* to represent the number of female deer for each age group, hence, N_t^0, N_t^1, N_t^2, N_t^3 and N_t^4:

$$\begin{pmatrix} N_t^0 \\ N_t^1 \\ N_t^2 \\ N_t^3 \\ N_t^4 \end{pmatrix}$$

Similarly, we can use a vector N_{t+1} to represent the female deer for each age group for the following generation $t+1$:

$$\begin{pmatrix} N_{t+1}^0 \\ N_{t+1}^1 \\ N_{t+1}^2 \\ N_{t+1}^3 \\ N_{t+1}^4 \end{pmatrix}$$

The example is concluded by relating the matrix L and the vectors N_t and N_{t+1} described above in a single expression using matrix notation. Now, in order to check the structure of the ages of the population from one generation t to another $t+1$ all we need to do is calculate the product of the vector corresponding to the generation t for the matrix L:

$$\begin{pmatrix} N_{t+1}^0 \\ N_{t+1}^1 \\ N_{t+1}^2 \\ N_{t+1}^3 \\ N_{t+1}^4 \end{pmatrix} = \begin{pmatrix} f_0 & f_1 & f_2 & f_3 & f_4 \\ s_0 & 0 & 0 & 0 & 0 \\ 0 & s_1 & 0 & 0 & 0 \\ 0 & 0 & s_2 & 0 & 0 \\ 0 & 0 & 0 & s_3 & 0 \end{pmatrix} \begin{pmatrix} N_t^0 \\ N_t^1 \\ N_t^2 \\ N_t^3 \\ N_t^4 \end{pmatrix}$$

In abbreviated form: $N_{t+1} = L \cdot N_t$.

Without entering into the details of matrix operations (which we shall cover in Chapter 4), let us assume that the experimental data available for the deer, organised into age groups, indicates a population structure in ascending order of age as follows: 190, 80, 56, 18 and 6, giving the matrix *L*:

$$\begin{pmatrix} 0.2 & 1.0 & 2.0 & 0.8 & 0.2 \\ 0.9 & 0 & 0 & 0 & 0 \\ 0 & 0.8 & 0 & 0 & 0 \\ 0 & 0 & 0.6 & 0 & 0 \\ 0 & 0 & 0 & 0.4 & 0 \end{pmatrix}$$

Multiplying the vector with the starting data by the matrix *L* gives the following vector:

$$\begin{pmatrix} N_1^0 \\ N_1^1 \\ N_1^2 \\ N_1^3 \\ N_1^4 \end{pmatrix} = \begin{pmatrix} 0.2 & 1.0 & 2.0 & 0.8 & 0.2 \\ 0.9 & 0 & 0 & 0 & 0 \\ 0 & 0.8 & 0 & 0 & 0 \\ 0 & 0 & 0.6 & 0 & 0 \\ 0 & 0 & 0 & 0.4 & 0 \end{pmatrix} \begin{pmatrix} 190 \\ 80 \\ 56 \\ 18 \\ 6 \end{pmatrix}$$

Multiplying the vector obtained using matrix *L* gives another vector that can once again be multiplied by the matrix *L*, and so on. After 10 units of time, repeatedly iterating the model, we find that the total population of deer is structured as follows, in ascending order of age: 48%, 29%, 16%, 6% and 4%.

Cellular automata

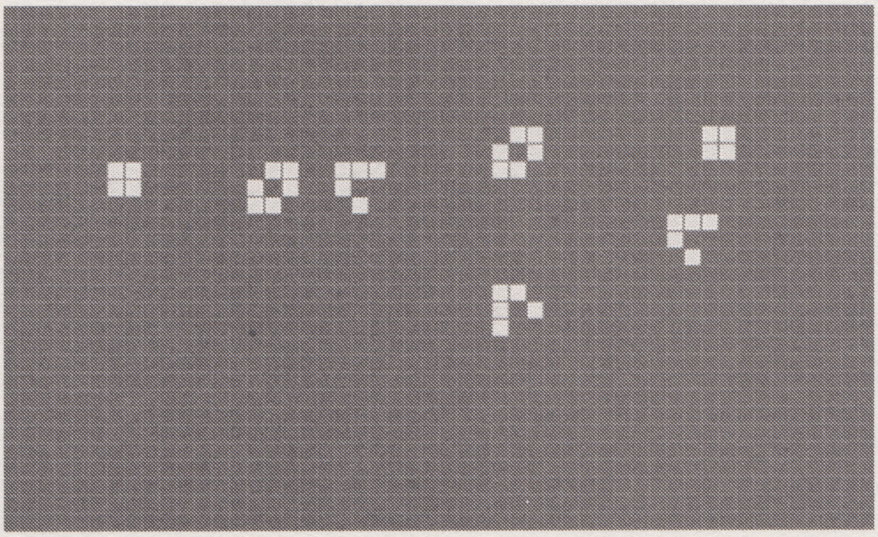
In the 1940s, two brilliant minds, Stanislaw Ulam and John von Neumann, introduced a modelling and simulation technique referred to as cellular automata. Ulam was researching the growth of crystals, whereas von Neumann was studying asexual reproduction from a theoretical perspective for the first time. He called it self-replication. Both met at the Los Alamos National Laboratory, where the first atomic bomb was being developed and where another genius of the time had also worked, Alan Turing.

John von Neumann, who, together with Stanislaw Ulam, created cellular automata.

Cellular automata are models that allow us to tackle the same type of problems as differential equations. However, they have a number of advantages, such as the fact that equations are not required for the phenomenon or system, they do not require a particularly powerful computer, and the results can be obtained quickly. Furthermore, the prediction of the future state of a phenomenon or system, or rather the solution that is sought, is represented in an eye-catching manner using graphs on the computer. Hence, for example, the reaction–diffusion model used by Turing to explain patterns in the skin of vertebrates, such as the stripes of zebras, can be simulated, and hence visualised, on a computer using cellular automata, without needing to make use of equations.

In 1970, Briton John Horton Conway popularised this technique by means of the so-called *Game of Life*. This automaton was – and remains to this day – so famous that it broke free from laboratories and appeared on many home computers. In 2002 Stephen Wolfram, one of the scientists involved in the study of cellular automata, and father of the Mathematica programme, wrote a controversial book entitled *A New Kind of Science*. In his book Wolfram also predicted the birth of a new type of physics with its foundations based on cellular automata.

At present, cellular automata allow us to simulate phenomena as diverse as the rings of a planet (for example, Saturn) a column of smoke (and hence, the aggregation of particles), the behaviour of a group of ants, the growth of a crystal, the patterns to be found on the skin of vertebrates and shells, and even the opinions of a group of people and their voting intentions for an election.



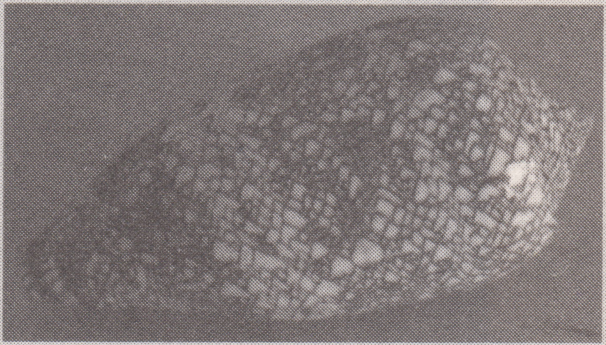
Screen shot showing some classic configurations from the Game of Life *invented by John Horton Conway. The various shapes and patterns that make up the automata represent alternative 'solutions' to those obtained using differential equations.*

A cellular automaton is a grid with cells that represent a certain state from a set of possible states. For example, if there are only two states, the cells can be in state 1 (black, or *on*) or 0 (white, or *off*). The cells are referred to as finite state machines. For example, a traffic light is a finite state machine with three possible states: green, amber and red (ignoring the red/amber combination. All cells have other neighbouring cells, often including a cell as part of the neighbourhood. Although there are many types of neighbourhood, one possible neighbourhood is that in which a cell's neighbours are those located to the north, south, east and west, including the cell itself.

In a given simulation, an initial state ($t = 0$) is defined for the cells on the grid, applying previously selected criteria. The state of the cells is then updated with their new state ($t + 1$), which has been obtained by applying previously specified rules that take into account the current state of the cell to be updated in addition to that of its neighbours. This process of updating is repeated until the simulation experiment is deemed complete. Patterns appear on the grid of the cellular automaton, which are often spectacular and which are interpreted as the solution, meaning that they will represent a 'radiography' of the future state of the system being studied.

CELLULAR AUTOMATA IN NATURE

A classic example of mathematical biology in action is the study of shells from the *Conus* and *Cymbiola* genera. Such shells have attractive patterns produced by activator and inhibitor pigments that appear to be governed by what is known as 'Rule 30', one of the rules studied by Stephen Wolfram. There is nothing strange about the fact that these shells are regarded as two good examples of cellular automata in nature.



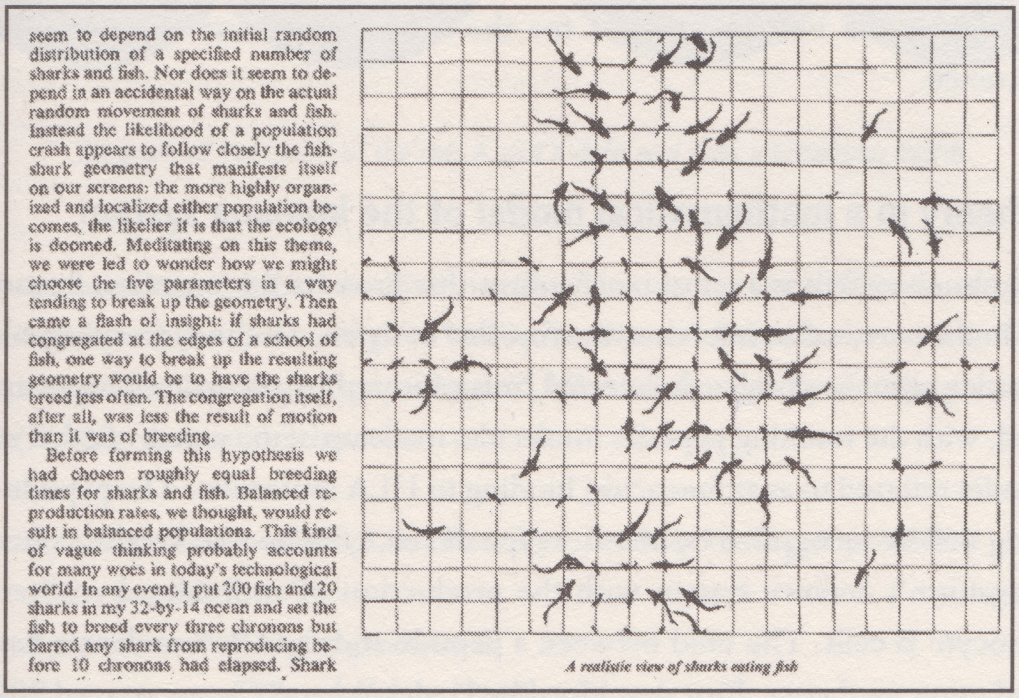
A specimen of Conus textile*; the lines on the shell follow a pattern similar to the one obtained using the 'Rule 30' cellular automaton.*

The predator–prey model using cellular automata

The Volterra–Lotka predator–prey model was one of the first mathematical models to be used in biology and is arguably one of the most famous in mathematical biology. As we have previously mentioned, one of the advantages of cellular automata is that it is not necessary to know the differential equation governing a certain phenomenon or system. One example of this possibility is the version of the Volterra–Lotka predator–prey model using cellular automata. The model was introduced in 1984 by A.K. Dewdney in his article *Shark and Fish Wage an Ecological War on the Toroidal Planet Wa-Tor.* Without using any of the equations devised by Volterra and Lotka, Dewdney was able to arrive at similar results using a standard computer from the 1980s. The aim of the experiment was to find the appropriate values for the parameters of a model that allowed the coexistence of two populations of predators and prey (sharks and fish, respectively), in the same grid. The parameters were:

- Number of prey (fish).
- Time threshold for the reproduction of prey. If a fish survives for a given number of cycles (or a predefined simulation time) and a cell is free, a fish will be born there.
- Number of predators (sharks).

– Maximum starvation time for predators. If a shark is unable to eat fish for a given number of cycles (or predefined simulation time) it will die.
– Time threshold for the reproduction of predators. The definition is similar, although the value does not have to be the same as the value for the fish.



seem to depend on the initial random distribution of a specified number of sharks and fish. Nor does it seem to depend in an accidental way on the actual random movement of sharks and fish. Instead the likelihood of a population crash appears to follow closely the fish-shark geometry that manifests itself on our screens: the more highly organized and localized either population becomes, the likelier it is that the ecology is doomed. Meditating on this theme, we were led to wonder how we might choose the five parameters in a way tending to break up the geometry. Then came a flash of insight: if sharks had congregated at the edges of a school of fish, one way to break up the resulting geometry would be to have the sharks breed less often. The congregation itself, after all, was less the result of motion than it was of breeding.

Before forming this hypothesis we had chosen roughly equal breeding times for sharks and fish. Balanced reproduction rates, we thought, would result in balanced populations. This kind of vague thinking probably accounts for many woes in today's technological world. In any event, I put 200 fish and 20 sharks in my 32-by-14 ocean and set the fish to breed every three chronons but barred any shark from reproducing before 10 chronons had elapsed. Shark

A realistic view of sharks eating fish

Part of Alexander K. Dewdney's article on the predator–prey model, published in the December 1984 edition of the journal Scientific American.

In his model, the grid, or rather the cellular automaton, is in the shape of a toroid, which creates an effect of continuity and eliminates edges, emulating the sea. Cells have only three states or colours, one to indicate they are occupied by a fish, another to indicate the presence of a shark, and another to indicate they are unoccupied or free. Fish (cells of a certain colour) 'swim' at random to one of the four neighbouring cells (north, south, east, west) if one or more are free (with no colour). A shark 'eats' a fish if it is in a neighbouring cell (a cell with the colour chosen for the fishes). If there are no fish in the surrounding cells, the shark will swim to a free cell.

The dynamic behaviour of a simulation experiment is similar to that obtained mathematically using the Volterra–Lotka equations. If there are few sharks, the number of fish will grow rapidly. If the population of fish suffers a large increase (remember they represent the food for the sharks) the latter will also grow in number, gradually reducing the population of fish. Depending on the quantity and distribution of sharks in the toroidal grid as the number of fish decreases, the fish may become extinct. Under these circumstances, only the population of sharks will remain and this too will quickly become extinct, as they will lack food, namely fish. Hence, what are the conditions of coexistence to prevent the aforementioned scenario occurring? We invite the reader to play Wa-Tor and discover the best parameters for the model to ensure the possibility of coexistence.

Set theory in a mathematical model of the immune system

The immune system is a set of mechanisms that protects the organism from infections. In the event of an infection, the first line of defence is the macrophages. Once an invader agent or antigen is detected, it is captured by the macrophages and destroyed, with the resulting peptides (molecules made up of the union of other smaller molecules referred to as amino acids) binding to HLA molecules. The peptide-HLA binding will be recognised by another type of cell, lymphocyte T cells, continuing the organism's defence system with the production of antibodies by other cells, lymphocyte B cells. The bind between a peptide and the HLA molecule has been studied using set theory. First developed by Dedekind and Cantor around 1870, set theory is a branch of mathematics that studies collections of objects. For a while it was a fashionable topic for teaching modern mathematics.

In set theory, a set is a collection of objects, or elements, that conform to a previously defined property. Let A be a set; an element x belongs to set A if x complies with a certain previously defined property P. Using mathematical notation: $A=\left\{x \middle| x \in P\right\}$.

Furthermore, if the elements of set A also belong to set B, A is a subset of B, written as $A \subseteq B$. There are two basic operations in set theory: union and intersection. The union of two sets A and B, written as $A \bigcup B$, is the set formed by all elements that are members of A and B, or both at the same time. For example, the union of {1, 3, 5} and {2, 4, 5} is {1, 2, 3, 4, 5}. Similarly, the intersection of two sets A and B, written as $A \bigcap B$, is the set of elements that belong to both sets A and B. For example, the intersection of {1, 3, 5} and {2, 4, 5} is {5}. Sets can be represented graphically using Venn diagrams, devised by John Venn in 1880. They are currently widely used in studies in linguistics, probability theory, logic and informatics.

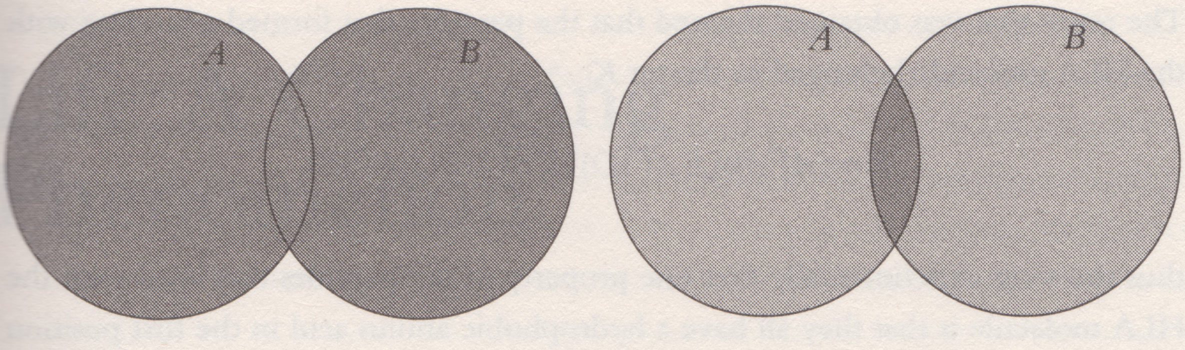


Diagram of the union of the sets A *and* B *(left) and their intersection (right).*

In an article published in 2008 in the Mexican journal *Ciencias de la salud* (*Health Sciences*), Javier Rodríguez Velásquez showed that set theory can be used to represent the binding of peptides and HLA molecules by devising a series of rules (R) that determine the sets:

- R_1: the presence of Val, Leu, Phe, Tyr, Ile, Met or Trp at position 1 of the peptide.
- R_2: presence of Arg at position 2.
- R_3: presence of Gly or Pro at position 3.
- R_4: presence of Ala, Val, Leu or Met at position 4.
- R_5: presence of Arg, Lys, Ser, Thr, Ala or Gly at position 6.
- R_6: presence of Asn, Gln, Leu or Met at position 7.
- R_7: presence of Ala, Leu or Met at position 9.
- R_8: presence of Phe, Tyr or Trp at position 1 and Asn and Leu in any other position.

The above rules can be used to define the following set. Let x be a peptide; x belongs to the set A if it complies with the first rule:

$$A=\left\{x\middle|x\in R_1\right\}.$$

A similar method is used to define the sets: $B=\left\{x\middle|x\in R_2\right\}$, $C=\left\{x\middle|x\in R_{44}\right\}$, $D=\left\{x\middle|x\in R_7\right\}$, $E=\left\{x\middle|(x\in C)\bigcap(x\notin D)\right\}$ and $F=\left\{x\middle|x\in R_8\right\}$.

Note that a peptide belongs to set E if it belongs to sets C and (intersection operator) does not belong to set D.

A total of 48 peptides were studied, 25 of which formed a binding with HLA. The result that was obtained showed that the peptides that formed a binding with the HLA molecule belonged to the set K:

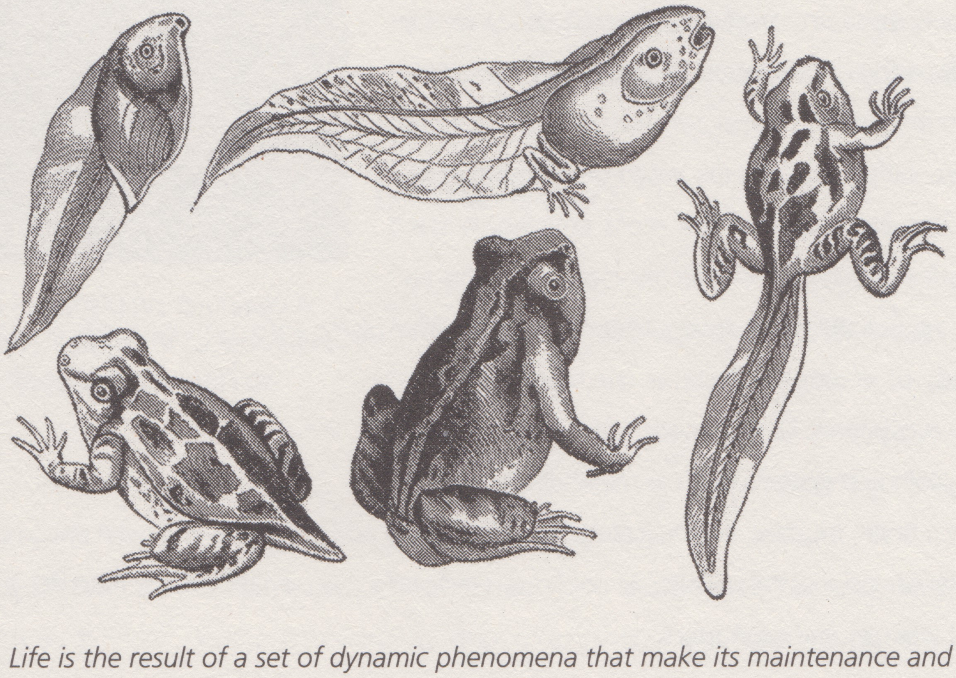
$$K=(A\cap B)\cup(A\cap D)\cup(A\cap E)\cup(B\cap F),$$

thus showing experimentally that one property of the peptides that bind with the HLA molecule is that they all have a hydrophobic amino acid in the first position (R_1) and Arg in the second position (R_2). Hence, written in set theory notation, we have $A\cap B$.

Chapter 2

Life: A Changing Phenomenon

Living things, or parts of them, appear to be involved in the most wide-ranging of tasks to keep the fascinating and complex phenomenon that is life afloat. Some examples of the dynamic behaviour of living things include the continuous to-ing and fro-ing of foraging ants, the motion of red corpuscles in the blood, the formation of flocks of birds, the ceaseless transformation of signals between the neurons of the brain, the transformation of certain substances into others by cellular metabolism, the beating of a heart, the stages through which an embryo passes before the birth of an individual, and the transformations experienced by a tadpole during its metamorphosis. These are changing systems, insofar as their situation, or their vital state or behaviour, changes over time. If we could observe everything that happens inside a simple cell during a one-second period, we would be amazed at all the transformations that take place. Such systems are described as being dynamic.



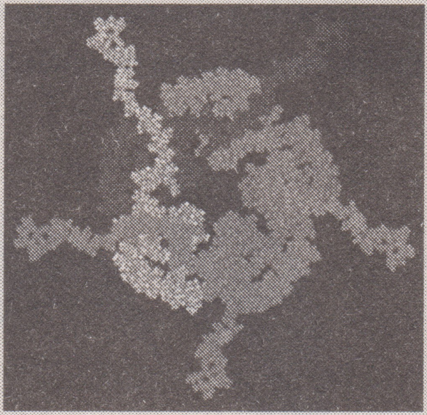
Life is the result of a set of dynamic phenomena that make its maintenance and perpetuation possible. The image shows the life cycle of frogs according to a German engraving from the end of the 19th century.

In the study of living things and ecosystems, it is possible to apply the same theories and methods used for any other system with dynamic properties. Hence, for example, biological systems are made up of a set of elements, such as ants, neurons, metabolic substances or birds, with the distinguishing feature that their behaviour or state (of the ant colony, brain, metabolism or flock of birds) changes over the course of time.

Another important property is that the behaviour or state of a system is the result of the relationships and interactions between its parts or elements. For example, the state of an ant colony at time *t* will be the result of the interactions between the ants at that moment in time. Based on this property, it is clear that a mathematical model must include those observable characteristics that represent the state or behaviour of the system under study. For example, in the case of the ant colony, the number of worker ants, soldier ants, etc., or in the example of the metabolism, the quantities of the metabolic substances *A*, *B*, *C*, etc.

PREDICTION AND SIMULATION

The idea of prediction has become firmly entrenched in the society of the 20th and 21st centuries, with the ability to control future changes – be they social, economic, epidemiologic or environmental – being decisive when it comes to the development of the human race. Since the invention of the computer, forecasting the future using simulation experiments based on a mathematical model has been one of the most commonly used techniques in science and technology. Its scope and interest ranges across all areas of human activity, from the study of ecological systems (such as population growth, ecosystems, climate models, the biosphere, etc.) and physiological systems (such as metabolism, cells, the heart, the brain, muscles, pharmacology, etc.) in biology and medicine, and even encompasses the study of social systems (such as opinions, electoral voting, employment, markets, etc.) in political sciences and economics.



A computer simulation of the behaviour of the proteins related to Parkinson's disease.

For mathematicians, the observable properties of a system whose value can be captured experimentally in the field or in the laboratory are the variables of the model, represented as $x, y, \ldots, z$. If the value of these variables is known over the course of time ($x(t), y(t) \ldots, z(t)$) we know the state or behaviour of the system (for example, the ant colony, the brain, the metabolism or the flock of birds) at time t. Note how in a dynamic system, time t is the independent or *input* variable and the *output* is the state of the system as defined by the set of dependent variables $x(t), y(t) \ldots, z(t)$. The mathematical model is not only useful for describing the state or *output* of a system at a given time t, but also for trying to predict its future state for a value of t sufficiently distant from the current one, as is the case in weather forecasts or during an epidemic. The forecasts for influenza, 'mad cow disease' and AIDS have been hot topics over recent decades, to name but a few.

Extracting the gift 'y' from the Easter egg

A classical mathematical problem is as follows: imagine we know the derivative of a certain function, but do not know the function from which the derivative was obtained. For example, $3x^2$ is the derivative y' of an unknown function y (in mathematical notation, $y' = 3x^2$). The question is: what is y? This function y, also known as a primitive, can be easily discovered by calculating the integral of the expression for the derivative: $\int 3x^2\,dx$.

First of all, we bring the 3, which is a constant, outside the integral: $3\int x^2\,dx$. Secondly since we are dealing with a standard integral, it suffices to recall that:

$$\int x^n\,dx = \frac{x^{n+1}}{n+1} + C,$$

where C is the integration constant. In our case this gives the following expression for y:

$$3\int x^2\,dx = 3\frac{x^3}{3} + C.$$

Simplifying and eliminating the 3 from the result gives the expression of the function y, $y = x^3$. Note once again that everything we have done has been part of a standard procedure for finding the expression $y = f(x)$ using the available information. That is none other than the expression corresponding to the derivative of the function $y' = f(x)$. We have been able to satisfactorily solve the problem by applying the procedure of integration.

However, what happens when y' is not directly expressed as $f(x)$. For example, we can see $y' = 3x^2$? There are numerous practical cases in which y' and y are contained in the same expression or equation, known as a differential equation. Hence, a differential equation is nothing more than an expression containing an unknown function y and its derivative y'. Furthermore, it contains the independent variable x, which in the case of dynamic systems is substituted for the time t. When writing equations of this nature, y' is replaced by its equivalent dy/dt. Hence, in its simplest form, a differential equation will be an expression of the type:

$$\frac{dy}{dt} = f\left[y(t), t\right].$$

However, let's take a step forward with the meanings of the terms contained in a differential equation. Specifically, what does y' mean (or what is dy/dt)? The derivative expresses the rate of change, ratio of change, speed or rhythm at which a system changes. Remember that one property of dynamic systems is that their state depends on the interactions between their elements and that any change that takes place in one element will affect the state of the system, y. In other words, if we know the state of a system at time t, for example $y(t)$, and we substitute its value in the differential equation, this gives a measurement of the change experienced by the system, the value of which is equal to y'. Note how the properties of differential equations make them the best and perhaps the most natural mathematical tool for mathematical models of dynamic systems because they contain everything required to create them. This underwrites their importance in mathematical biology, where they have been used to model many biological and ecological phenomena, as we shall see throughout this chapter.

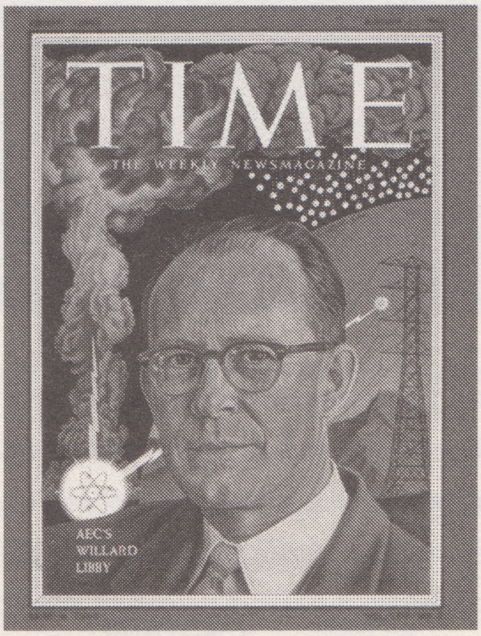
But how can we find y in a differential equation? The problem is not as simple as the example in which, given the derivative $y' = 3x^2$, it is possible to directly obtain y by integration. When it comes to differential equations, we need to make use of the expression of the differential equation and not just the derivative y'.

If we compare the expression of a differential equation to a chocolate Easter egg with a small toy inside, solving the equation consists of getting our hands on the gift y by the step-by-step manipulation of the expression or chocolate egg. For example, the first step is to remove the wrapping, before eating the chocolate until finally reaching the gift – or expression y. Solving a differential equation is nothing more than finding the expression of y. Manipulating the Easter egg 'by hand', or if we prefer, 'using a pencil and paper', by applying a set of methods or procedures, will give y through the application of analytical methods for solving the equation.

However, at some point, we will need to make use of integration. Alternatively, it can be solved using a computer, with various techniques available to find y, such as the popular methods of Euler and Runge-Kutta. These techniques are known as numerical integration methods in pharmacological laboratories and computer-based ecological studies. They owe their popularity to the large number of programs available for solving differential equations in practically any programming language (C/C ++, Java, Visual Basic, etc.).

The differential equation from *Jurassic Park*

In the 1950s, Willard Libby devised an ingenious system for providing the approximate date of a fossil. Libby's method was based on measuring the quantity of radioactive carbon-14 (C-14) present in the fossil or any organic object in question, including the Shroud of Turin.



The American chemist Willard Libby (1908–1980) on a commemorative cover of Time *magazine.*

C-14 is an isotope, the quantity of which is constant in the Earth's atmosphere. Living things incorporate C-14 throughout the course of their lives, either by breathing or eating other living things. Regardless, and independent of how it is incorporated, the quantity of C-14 is also constant in living organisms. However, when something dies, it ceases to absorb more C-14 and it begins to gradually decay into other elements.

We shall use the expression for the solution to the Malthusian growth equation to obtain an expression that allows us to date an object. In this case y will be the quantity of C-14 at a given time t, where y_0 is the quantity of C-14 measured in the fossil. The expression also includes r, known as the decay constant and which has been established for each isotope: $y = y_0 e^{rt}$.

Given that it is known that C-14 has a half-life of 5,600 years this must be substituted into the previous expression:

$$\frac{1}{2} y_0 = y_0 e^{5.600r}.$$

Applying a series of operations gives: $y = y_0 e^{-0.00012378t}$, and solving for time t gives the formula used by palaeontologists and archaeologists to date fossils and any other discoveries of historical interest:

$$t = \frac{\ln(c)}{0.00012378}.$$

The expression above can be used as long as the object is no older than 50,000 years.

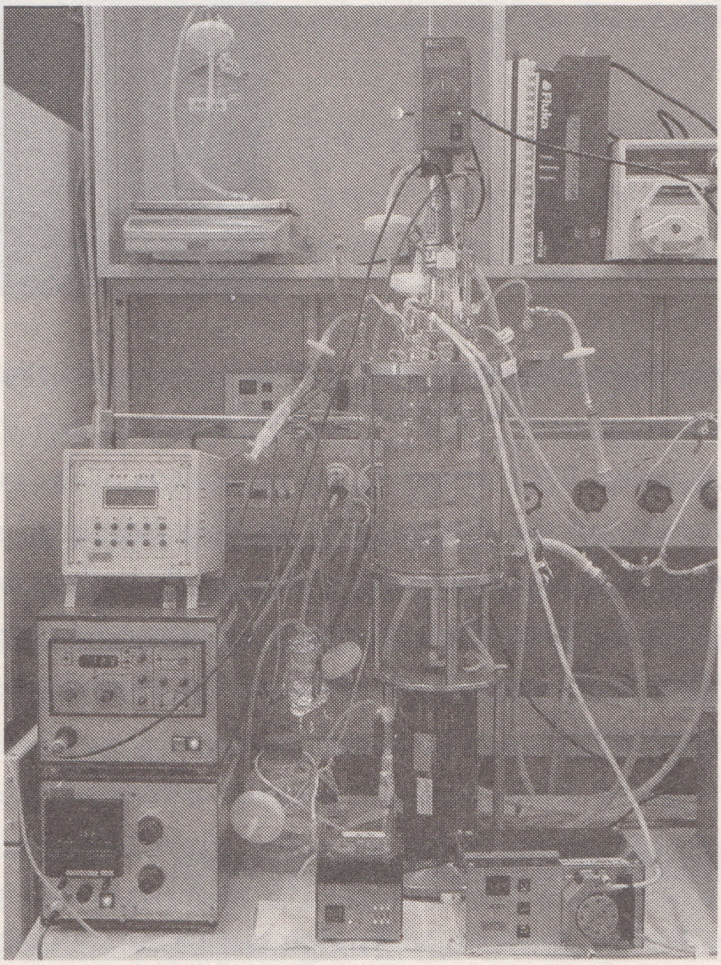
For example, if we find a prehistoric animal bone with 1/100 of C-14 left, how old is the fossil? According to the information, c is equal to 100; substituting this into the expression gives:

$$t = \frac{\ln(100)}{0.00012378} = \frac{4.60517018}{0.00012378} \approx 37{,}204$$

allowing us to conclude that the bone is approximately 37,000 years old.

Differential equations in biotechnology

Biotechnology is an area of biology in which the techniques of genetic engineering and cell cultures are applied to numerous problems in agriculture, pharmacology, medicine and nutrition. One of the most commonly used devices in biotechnology is the chemostat, a tank or bioreactor used for the production of useful substances from a culture of microorganisms.



A laboratory bioreactor loaded with bacterial cells.

The idea is to ensure the number of microorganisms N and nutrients C are 'almost constant', keeping the microorganisms in exponential growth. The reason for maintaining this growth pattern of microorganisms is that it allows them to produce useful substances, such as antibiotics. Nutrients must be continually provided, eliminating liquid, toxins and any other substance produced by the microbial metabolism at the same time, keeping the volume of the culture medium constant. In industry, the chemostat is used to produce substances such as ethanol, fermented foodstuffs like cheese, and complex proteins with therapeutic value, such as insulin. It is also used in research for studies on the ecology of microorganisms, as well as for studying the evolution of bacteria and other microorganisms. Although we shall avoid going into detail here, differential equations have been applied successfully to bioreactors. Hence differential equations are the tool used by biochemical engineers and other biotechnicians for their work. The handling and application of these equations is a specialism of mathematical biology. For example, in the case of the chemostat, the differential equations that describe its operation are:

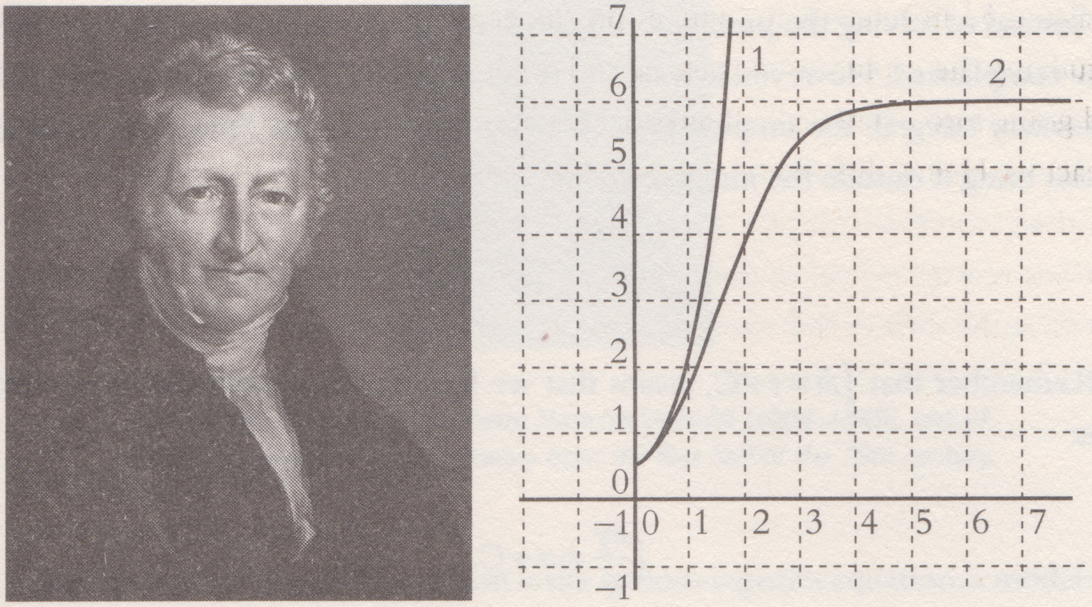
$$\frac{dN}{dt} = K(C)N - F\frac{N}{V},$$

$$\frac{dC}{dt} = -\alpha K(C)N - F\frac{C}{V} + F\frac{C_0}{V}.$$

where N is the number of microorganisms, C is the concentration of nutrients, F is the flow (with F equal to $F_{\text{input}} = F_{\text{output}}$ in the chemostat) and V the volume. In the differential equations $K(C)$, α and C_0 are parameters of the model. Note that the expression that models the rhythm of N, the first differential equation, recalls the logistic equation. It is into this equation that the flow F has been introduced. A variety of software has been developed for controlling the chemostat based on these equations. One application of this software, for example, is controlling fermentation with a computer.

Malthus, Verhulst and population growth

In 1798 Thomas Robert Malthus, an English clergyman, published his *Essay on the Principle of Population.* According to his conjecture, it may be the case that the number of humans increases numerically in a geometric progression – in other words, exponentially. However, he then identified a problem. Food resources grow arithmetically, or linearly. (This can be extended to apply to any resource.) Hence, the number of human beings will increase in the following way, 2 (2^1), 4 (2^2), 8 (2^3), 16 (2^4), 32 (2^5), 64 (2^6), etc., whereas the food available will increase as follows, 2, 3, 4, 5, 6, etc. Consequently, according to the famous vicar (incidently despised by Marxists, who regarded his theories as an attack on the working class) predicted we shall reach a situation where birth rates – especially among the working classes – will outstrip the amount of food available, resulting in mass starvation.



The Anglican cleric Thomas Robert Malthus (1766–1834) and the two models of growth: exponential (1) and linear (2).

Let us assume we apply a Malthusian model, specifically $y' = ry$ to a population that need not necessarily be human – other animals or microorganisms work just as well. Note that, ultimately, the Malthusian model of growth means the speed or rhythm y' (which is the rate) at which a population grows is proportional to its current size y. Hence, using a little mathematical cunning, it is possible to reorganise the terms of the differential equation as shown below. Firstly, the expression is rewritten as follows: $dy/dt = ry$, where r is the parameter expressing the birth or incorporation of new individuals at a constant rate, generation after generation, referred to as the specific population growth rate or ratio.

Secondly, we bring dt to the right, to give: $dy = rydt$. Now, if we consider the way in which this expression is written, it looks as if it is 'begging us' to regroup all the terms relative to y. Hence, we can move y to the left, to give: $dy/y = rdt$.

Finally, and in order to solve the expression, we integrate both terms, on the right and the left, as shown below:

$$\int \frac{dy}{y} = \int r\,dt.$$

It is possible that upon reaching this point we will be left with the impression that instead of solving the problems of microbiology, the argument is making things more complicated. However, let's analyse the expression. The term on the right is the elementary integral, the simplest possible of standard integrals. Since r is a constant, we can bring it outside the integral, giving:

$$\int \frac{dy}{y} = r \int dt.$$

Remember that $\int dt = t + C$, means that we have already solved the term on the right:

$$\int \frac{dy}{y} = rt + C.$$

The term on the left is also a classic standard integral. Note that since dy is the numerator and y is the denominator, the integral is the logarithm of y, in other words:

$$\int \frac{1}{y} dy = \ln(y) + C.$$

Hence,

$$\ln(y) = rt + C.$$

Removing the logarithm and reorganising the terms gives the solution to the differential equation $y' = ry$. We can now introduce the initial quantity of bacteria – previously represented as y_0 – to give the expression for y, hidden in the Easter egg:

$$y = y_0 e^{rt}.$$

In 1838 Verhulst modified the Malthusian growth expression, introducing the requirement for a maximum population or a value k, known as the 'carrying capacity', since the space or environment that supports it is limited. All this resulted in the following differential equation:

$$y' = ry\,(k-y).$$

The Belgian mathematician Pierre Francois Verhulst (1804–1849), one of the great experts in number theory from the first half of the 19th century.

The solution to Verhulst's equation is the famous logistics equation, a model that, in addition to population growth, can also be applied to epidemics and the size of social networks on the Internet, such as Facebook:

$$\gamma = \frac{k\gamma_0}{\gamma_0 + (k - \gamma_0)e^{-rt}}.$$

The logistics equation is useful in 'S-shaped' growth phenomena. It is a bounded exponential growth model, meaning that the growth comes to a halt because the resources favouring it are limited, whether these are physical space or food, mobile telephone customers or members of a social network. On the other hand, exponential growth is a model of unlimited growth since there are no limits to resources. That means that while the exponential model assumes individuals are in an ideal world with inexhaustible resources, a veritable 'Garden of Eden', the logistical model deals with the real world, with planet Earth, where resources are obviously scarce.

It is perhaps curious to note that these types of models were proposed in the 19th century, at the height of the industrial revolution. The period also saw scientists such as Charles Darwin, father of the theory of evolution and natural selection, and Charles Babbage, who invented the Analytical Engine and Difference Engine, precursors to modern computers. These coincidences were the harbinger of a fertile collaboration between mathematics and computers, which became decisive in the study of life during the 20th century. By means of example, in the following sections we shall explore the way in which two of the greatest ailments suffered by the human being, cancer and viral infections, are tackled with the help of mathematics.

The mathematical study of cancer: tumours on the computer

Cancer is an illness in which a group of cells grows in an uncontrollable manner, normally forming a tumour that destroys nearby cells and tissues. In fact, a tumour includes normal cells, as well as cancerous cells, the latter being derived from a normal cell after a malign transformation process. As it is a classic illness, cancer has been one of the most heavily studied subjects in mathematical biology. Its importance is such that there is currently a database called the QCDB (Quantitative Cancer Modelling DataBase) that stores the information available on the illness for the use of biomathematicians throughout the world.

Mathematics is applied to the study of cancer by using mathematical models and carrying out computer simulation experiments. Mathematics has made a twofold contribution to the fight against this illness. On the one hand, mathematics helps when it comes to proposing a new hypothesis or conjecture on the causes that lead to the formation of a tumour. On the other, the use of mathematical models makes it much easier to bring together, and hence understand, the abundance of available experimental and clinical data.

At present, biologists and mathematicians deal with tumours as complex systems. This means a tumour is regarded as a dynamic system in which cancerous cells interact with each other and the other elements that are present, giving rise to behaviours that cannot be explained by isolating the cells of the tumour and analysing them separately. According to this approach, a tumour is not the result of the failure of a specific gene, or rather a gene that works incorrectly. At present, cancer is regarded as a collective failure caused by a large number of interactions between malfunctioning genes. Hence, using the Internet as an analogy, cancer would be the result of the failure of a large number of machines on the network (DNS servers, routers, etc.) that 'work together', as opposed to the failure of an individual machine.

In 1964 a researcher named Laird observed that when the growth of tumours occurs under limited conditions of space and food, it conforms to the famous Gompertz growth equation. A classic example of this is breast cancer. According to this differential equation, the rhythm or speed y' at which the size y of a tumour increases under these circumstances – a size that can be expressed in terms of its volume or, if we prefer, by the number of cells – is modelled using the following differential equation:

$$y' = \alpha \log\left(\frac{K}{y}\right) y.$$

In this expression, α is a parameter related to the ability of the cancerous cells of the tumour to proliferate, and K is the maximum size that can be reached by the tumour, since, let us recall, the available tissue is limited, as is the quantity of nutrients. Solving the differential equation gives the solution, which in this case corresponds to the Gompertz law of growth. The law was proposed in 1825 by the British mathematician Benjamin Gompertz as a refinement of the Malthusian model, and was first used by insurance companies. The idea underpinning Gompertz' law is that the increase in the rate of mortality conforms to the geometric progression based on age. Out of curiosity, Gompertz described the relationship between the rate of mortality, which we shall refer to as R_m, and age, or time t, by means of the following equation:

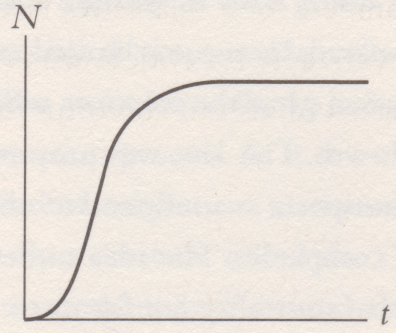
$$R_m = R_0 e^{\beta t} + A.$$

The curious thing about this expression is that the term A plays a surprising role in the model. It represents the effect of factors that are not related to the age of a person on the rate of mortality. For example, the increase in life spans in advanced countries is a result of being able to considerably reduce the value of A. This reduction has been possible thanks to increasing standards of living, which has resulted in a healthier living environment for people. Some factors that have influenced the reduction of A include the construction of cities and more comfortable buildings in which humans are better protected from the inclemencies of the climate, and improvements to hygiene and diets, etc. However, β, the parameter known as the Gompertz gradient, remains unmodified. Coronary diseases and cancer are responsible for the fact that, in spite of having achieved reductions in R_m through policies that have resulted in the reduction of A, R_m continues to increase with age to this day. Will we manage to eliminate or significantly reduce the effect of age or t on R_m one day?

If we apply Gompertz' law in a different context, specifically that of cancer, the size y of a tumour will thus be given by the expression:

$$y = Ke^{\left(\log\left(\frac{y(0)}{K}\right)e^{-\alpha t}\right)}.$$

where $y(0)$ is the initial size of the tumour. According to this model, if the patient is undergoing treatment, $y(0)$ will be less than K, otherwise its size will be larger.



Gompertz' curve for the growth of a cancerous cell
(N *is the size of the tumour and* t, *the time).*

It is a sigmoid shaped function highly similar to the logistical function, with which it shares the peculiarity that the growth is slower towards the start and end of the process. At the end, the deceleration in the growth of the tumour is obvious if we bear in mind, for example, that as its size increases, the cells deeper inside receive less oxygen, die out and cause necrosis in the nucleus of the tumour. Its size stabilises when the growth rate of the outer area is equal to the death or necrosis inside the tumour.

The growth dynamic of certain companies, specifically those with a strong technological component, such as pharmaceuticals, mobile telephony, etc. also conforms to this law. To begin with, the costs of research, patents, etc. outweigh sales. However the company then goes on to experience a period of considerable growth and profit. Finally, there is a stage in which sales diminish, as the market becomes saturated. Another example, which is particularly relevant to mathematical biology, is the growth of organs in an embryo, which also conforms to Gompertz' law. And perhaps more curiously, when a lizard loses part of its tail, its regeneration also conforms to this law.

Although the expression we have obtained above may appear complex, we should bear in mind that these sorts of expressions can be relatively easily operated using computers. In fact, it is an expression whose difficulty of calculation lies in the format in which it is presented. Rather, it is an expression of the form $y = ae^{be^{ct}}$, in which one exponential forms part of, or is nested within, another.

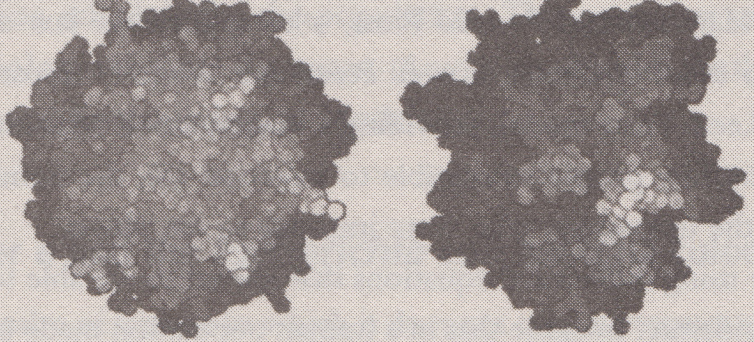
In the 1980s, a researcher named Wheldon observed that the growth of small tumours did not fit this law very well, and furthermore the law did not account for biological aspects, such as the role played by the immune system. Wheldon's refinement takes into account that at the beginning of the growth of the tumour, the cancerous cells do not compete for available resources, exhibiting exponential or Malthusian growth. However, there is a critical size for the tumour, above which growth is no longer Malthusian and instead conforms to Gompertz' law.

AIDS, swine flu and other epidemics that can be treated using mathematics

In 1983, French researcher Luc Montagnier discovered HIV (Human Immunodeficiency Virus). It is spherical and has a diameter of 100 nanometres, including an

MATHEMATICS AND NEW LINES OF RESEARCH

In 2005, a researcher at the Universidad Complutense de Madrid, Antonio Brú, proposed that in its advanced stages cancer could be treated and cured, causing a persistent and long-lasting peritumoral inflammation. The idea was the result of mathematical studies on the growth of tumorous cells, in which it was observed that all the cells grew according to the same pattern, which Brú called the universal dynamic of tumour growth. In this model, the activity of the cells bordering the tumour was of paramount importance, and Brú based his proposal for treatment on these peripheral cells. For a large part, the controversy caused by this proposal is due to the fact that the model differs from classical mathematical models of cancer in two aspects. Firstly, it assumes growth is not exponential but linear, and secondly, that growth is not governed by the nutrition 'sought' by the cancerous cells, but by space. It is a good example that illustrates how mathematics was able to suggest new lines to researchers when it came to the search for treatments for an illness that has claimed the largest number of victims in history: cancer.



A mathematical model and computer simulation of the growth of a tumour.

outer shell of proteins. It is what virologists refer to as a retrovirus, since its genome is made up of an RNA chain. According to information from the World Health Organisation, there were around 33.3 million people infected with HIV in 2009. The fact that 23 million of these sufferers were from sub-Saharan Africa, in addition to the main transmission mechanisms of the virus (specifically unprotected sex, mother-child transmission or through contact with the blood of an infected person) has been, and continues to be, part of the controversy that has accompanied this illness since its discovery.

In 2009, news of a new pandemic appeared in the media, the now famous swine flu. According to the WHO, the virus in question was H1N1/09, and its genetic material, or genome, was actually a mixture of bird, swine and human material. It is believed that the virus jumped between species, perhaps during intensive pig farming. Swine flu was the top news story throughout the summer and autumn of 2009 in all media outlets. At first, it appeared to be highly lethal, although this fear reduced with time as the scale of non-clinical cases was determined and with the application of anti-viral treatments.

Pandemic illnesses of this nature cause controversy and alarm. However, how are health authorities throughout the world able to predict and monitor them? How is it possible to know precisely that we are dealing with an epidemic from one country to the next? When should people who belong to a specific risk group be vaccinated? Essentially, this information is provided by a series of mathematical models that make up the formal core of epidemiology, which studies the factors that affect health and illness in human populations. Given its importance to health, epidemiology has attracted the attention of mathematicians since the start of the 20th century and is currently a strong research area in mathematical biology.

The pioneering researchers who applied a mathematical approach to epidemics where William Hammer and Ronald Ross, who applied the law of mass action to the behaviour of an epidemic. Lowell Reed and Wade H. Frost subsequently developed the Reed–Frost model, providing a mathematical relationship between the number of healthy people susceptible to infection (S), the number of people infected (I) and the individuals who were immune to the illness.

It is precisely using differential equations that specialists are able to evaluate the progress of an epidemic. Imagine that in a human population made up of a total of N individuals there are I people infected by a virus. This means that the number of healthy people, or rather those who are not infected, is $N - I$. Given that the infected people, of whom there are I, live together with the remainder of the population, or rather the people who are not infected $N - I$, the latter represents the healthy people susceptible (S) to infection. Hence, we can say that $S = N - I$.

One of the classic models from epidemiology states that the rate at which the number of infected people changes over time is expressed by the following differential equation: $I' = kI\,(N - I)$, which can be simplified to, $I' = kIS$. The solution to this differential equation is the famous logistical equation, to which epidemics conform. It is expressed as:

$$I = \frac{NI_0}{I_0 + (N - I_0)e^{-kNt}}.$$

Note that at the beginning of an epidemic, or rather when in mathematical terms t is small, or more precisely it 'tends to zero', the logistical equation approaches what is called exponential or Malthusian growth. This is why the number of people infected increases so quickly at the start of an epidemic. This means that in the case of illnesses that cause alarm among society, such as AIDS or swine flu, news stories about the rise of new cases accumulate in the media, further increasing the alarm.

Assuming that the limit of infections is given by all those susceptible but still healthy, or rather, $N - I$, there will come a point at which the epidemic will begin to decelerate, with the rate of new people infected I falling naturally. It is clear that this value, desired so badly by the health authorities of the country, has been reached when the number of infected people I is half the total population, specifically $N/2$. The number of new cases will then stabilise until the epidemic is over.

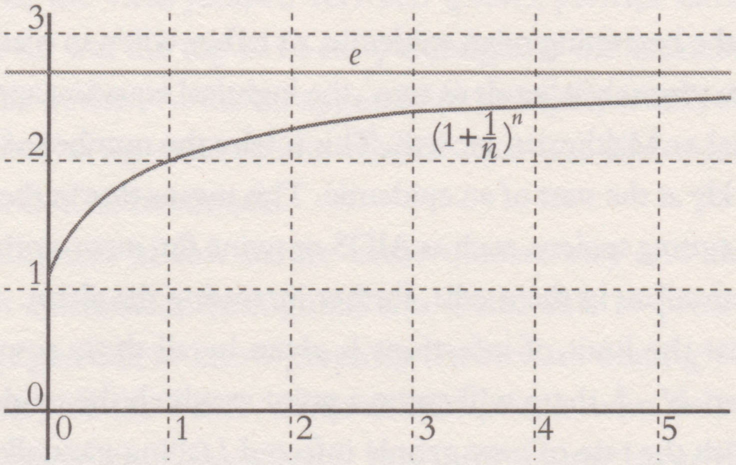
At present, and with the help of a computer and models similar to the one described, it is possible to mathematically evaluate the progress of an illness in a country, such as seasonal flu, which allows health authorities to manage the vaccination schedule for the population. The computer programmes used for epidemiology include Epigrass, AnyLogic Model-Builder and STEM (SpatioTemporal Epidemiological Modeler).

The number e and the *Escherichia coli* bacteria colony

There is no realm of science in which it does not crop up sooner or later, regardless of whether we are dealing with molecular biology or statistics, physics or chemistry – the number e is a 'demon' that is present in many natural phenomena. The number *e* is one of the so-called irrational numbers, since its decimal never ends and is without repetitions, a feature shared with with π. It is believed that the number *e* was discovered by Jacob Bernoulli as part of his studies of the limit:

$$\lim_{n\to\infty}\left(1+\frac{1}{n}\right)^n,$$

which gave the result of 2.71828. Using a symbolic computation program, such as Derive, we can immediately calculate the limit: LIM((1 + 1/n)^n, n, INF, 0), which gives us the previous result.



An approximation of the number e.

In 1618, the number had already figured in Napier's logarithm tables, and it is the base of the Naperian, or natural logarithms, $\log_e(x)$, abbreviated as $ln(x)$. It was the mathematician Euler, who gave it the name *e* in 1727. Among the curiosities surrounding this number, those related to the exponential function e^x are of particular interest. In the first place, the derivative of $f(x) = e^x$ is the function itself, or rather, $f'(x) = e^x$. Furthermore, taking the derivative at point $x = 0$ gives $f'(x) = 1$. Secondly, the same thing happens for the integral of the function, since $\int e^x\,dx = e^x + C$. Thirdly, adding together the infinite terms of the following series $1/0! + 1/1! + 1/2! + \ldots + 1/n!$ gives the number *e*.

Note how the denominators of the terms of the series are factorials of a number, such as, 4!, $4 \cdot 3 \cdot 2 \cdot 1$. However, if the series is $1 + x + x^2/2! + x^3/3! + x^4/4! + \ldots + x^n/n!$ the sum approximates to the exponential function e^x.

It occurs naturally in many phenomena. This is the case with exponential population growth, as studied by Malthus. An illustrative example of exponential growth is the growth of a colony of bacteria. Let N_o be the initial number of *Escherichia coli* on a Petri dish (a laboratory receptacle in which bacteriologists cultivate bacteria) and r be the rate of population growth, hence the number of bacteria in the colony N_t at time t is given by the following equation:

$$N_t = N_0 e^{rt}.$$

Given that the generation time for bacteria can be around 30 minutes, it will not be long before there are millions of bacteria on the Petri dish.

Another example of practical interest in mathematical biology is the Poisson distribution, which is related to the law of probability for describing random events with low probabilities. As an example, imagine the Petri dish with a culture of *Escherichia coli* bacteria. If we shine an ultraviolet light on the dish, the probability of obtaining a certain number of mutations (created by the high-energy light), x will be equal to:

$$p(x) = \frac{e^{-\lambda}\lambda^x}{x!},$$

where λ is the parameter of the law of probability. It also appears in hyperbolic functions, that have numerous applications in biology.

Chapter 3

Microbiology Succumbs to Chaos

Imagine a microbiologist wants to carry out a series of experiments for which they require a quantity of bacteria from the *E. coli* species. To get the required bacteria, they create a culture in a Petri dish, in line with standard procedures. Assume that the dish is inoculated with an initial quantity of bacteria, which we shall call y_0. Modern mathematical biological theory states that the growth of a population follows or conforms to the differential equation $y' = ry$. This means that the speed y' at which a bacterial culture grows, or rather the number of bacteria, is equal to the number of bacteria present in the culture at time t multiplied by r, where r is the instantaneous growth rate.

It is important to note that the bacteria will grow at the rate indicated in the differential equation as the food present in the culture medium does not run out. This condition can be achieved in a laboratory by making use of a chemostat, as we saw in the previous chapter. The physical space available must not represent a restriction to growth. This means that, theoretically, the bacteria must have an unlimited amount of space for all the new bacteria that will be formed, generation after generation. Where these conditions are met, we would be dealing with what is known as Malthusian growth, proposed by Malthus in 1798.

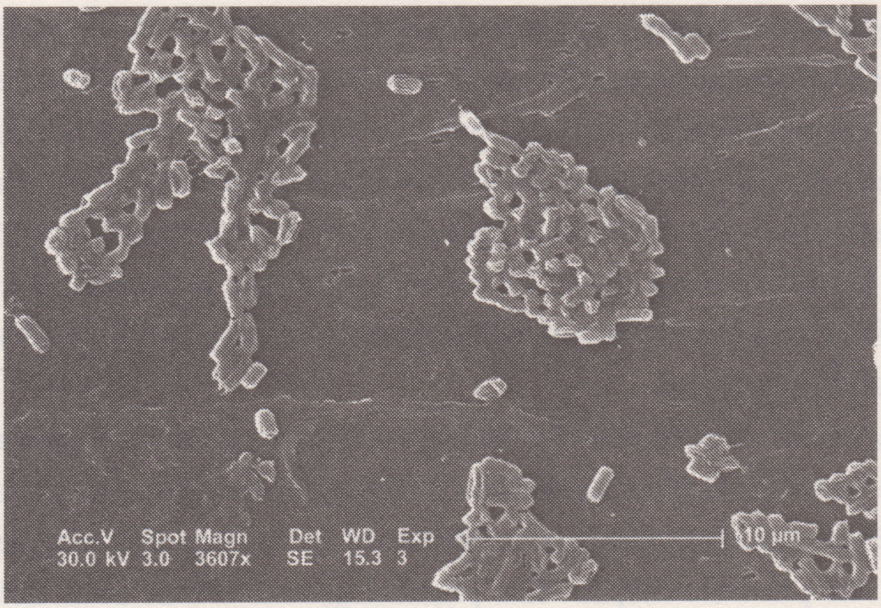
The differential equation $y' = ry$ and its limits

Solving the differential equation $y' = ry$, gives the following solution:

$$y = y_0 e^{rt}.$$

This expression tells us that the number of bacteria y at a given point in time t will be equal to the initial number y_0 multiplied by an exponential term. The exponential term is the number e, raised to the product of r and the time t. With respect to the value of r, this is a parameter, or in other words a property that cannot be observed directly. Its value can be determined in the laboratory through estimates or looked up in a manual. Remember that the number e is like π – it belongs to the group of irrational numbers. Its approximate value is 2.71828.

Note that the growth rate of the number of bacteria is exponential if the aforementioned properties hold. Using the expression provided at the start of this section, the microbiologist can determine how long he or she will need to wait to obtain a culture with the number of bacteria required by their experiment.



A scan showing the growth of a group of Escherichia coli *bacteria.*

Obviously, all of the above only holds if the microbiologist is able to supply a culture of *E. coli* with an unlimited amount of food and to all intents and purposes unrestricted growing space. However, in practice it is hard to ensure this last condition. With this in mind, the microbiologist is able to calculate the maximum number of bacteria that can be hosted by a laboratory receptacle, a parameter that we shall refer to as k. This parameter, the maximum population size, is also known as the carrying capacity. Hence the Malthusian growth expression $y' = ry$ must be modified, multiplying it by $(k - y)$. This gives a new differential equation that takes into account the restriction of the maximum population – the size that can be hosted by a certain environment:

$$y' = ry(k - y).$$

As we noted in the previous chapter, this expression is referred to as the Verhulst equation and was devised by the Belgian mathematician in 1838. It is clear that if the number of bacteria y increases, $k - y$ falls, and conversely, if the number of bacteria y falls, $k - y$ increases, thus regulating the size of the population. The regulation mechanism is similar to how a thermostat regulates the ambient temperature of a room, and represents the concept of feedback.

Note that in the specific case of bacteria – and in fact many other living things – the maximum number of individual specimens can be in the millions, and it is extremely inconvenient to work with numbers this large. For this reason, there is nothing to stop us defining the maximum number of individual specimens as 1 to make life easier, knowing that in fact the number will be arbitrarily large. Carrying out this change of scale, the population will oscillate between 0 and 1 (e.g. 0.67, 0.16, etc.), values that can be translated to the real size of the population if we know the scaling quantity represented by the unit. Taking into account this change of scale, the expression for our differential equation becomes:

$$y' = ry(1 - y).$$

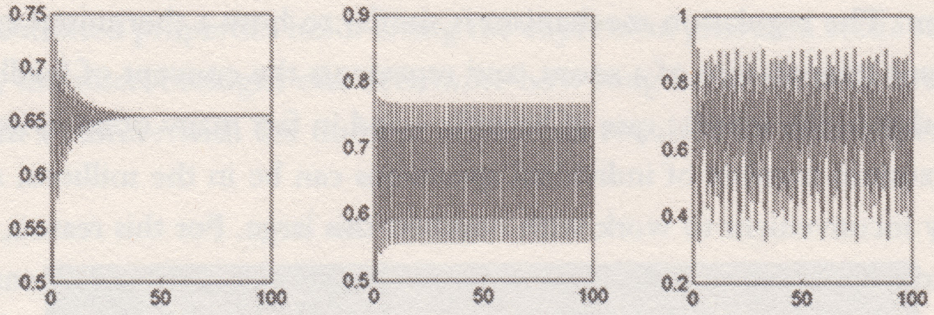
Before carrying out experiments with this equation, let us take one final step: substituting y' for $y(t + 1)$ and y for $y(t)$, the number of bacteria at future time $t+1$ and at present t, respectively. Rewriting the differential equation once more gives what is known as a difference equation:

$$y(t+1) = ry(t)(1 - y(t)).$$

As we can see, this expression can be handled easily using a computer. The expression was used by the biologist Robert May in 1976 to simulate population growth.

Four example experiments

Let's now imagine that the microbiologist carries out four experiments on their computer, numbered 1, 2, 3 and 4, where r – the instantaneous rate of growth – is 0.4, 2.4, 3.0 and 3.6, respectively. In all the experiments, we start with the same initial number of bacteria $y(0)$. For example, imagine that the receptacle is initially inoculated with a number of bacteria equal to 70% of the maximum population size 1 for that receptacle. Hence, $y(0)$ will be 0.7. Note that the only parameter that changes in the experiments is the value of r, providing a graphical representation at each time t for the number of bacteria $y(t+1)$.

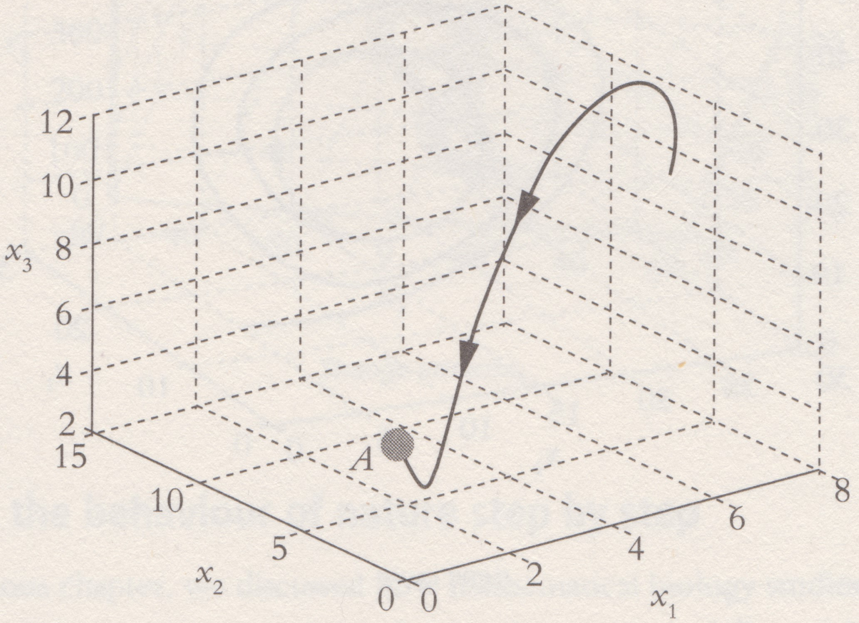


Graphs corresponding to the growth experiments for Escherichia coli.
From left to right, experiment 2 (r = 2.4), experiment 3 (r = 3.0) and experiment 4 (r = 3.6).

Experiment 1 uses the value $r = 0.4$. First, we calculate the number of bacteria after one unit of time using the difference equation $y(1) = 0.24y(0)(1 - y(0))$, substituting $y(0) = 0.5$. Once we have obtained $y(1)$, we calculate the number of bacteria after two units of time $y(2)$, or rather, $y(2) = 0.24y(1)(1 - y(1))$. We now obtain the values $y(3)$, $y(4)$ and so on, until a value of time t that can be as large as we wish. For example, let's study the growth of the population up to $t = 100$ units of time, at which point the number of bacteria will be $y(100)$. Finally, for each unit of time t we represent the number of bacteria $y(t)$. Note that given the initial value of the number of bacteria, $y(0)$, and a given value of the parameter r, we can use a computer to obtain a sequence of the number of bacteria at different times $y(0)$, $y(1)$ $y(2)$..., $y(100)$, a sequence of values referred to by mathematicians as an orbit. The question now is what is the tendency of the orbit? In other words, what is the final destination of a population?

To answer this question, the previous protocol is applied to the remaining experiments, although the calculations are carried out using the corresponding value of r. What happens? In experiment 1, the bacteria population dies off, meaning that after a certain period of time there will be no bacteria in the receptacle. However, from a mathematical point of view, we say that the population has reached its equilibrium, which occurs when the number of individuals does not vary and, hence, the rate of change y' (the same as dy/dt) is 0.

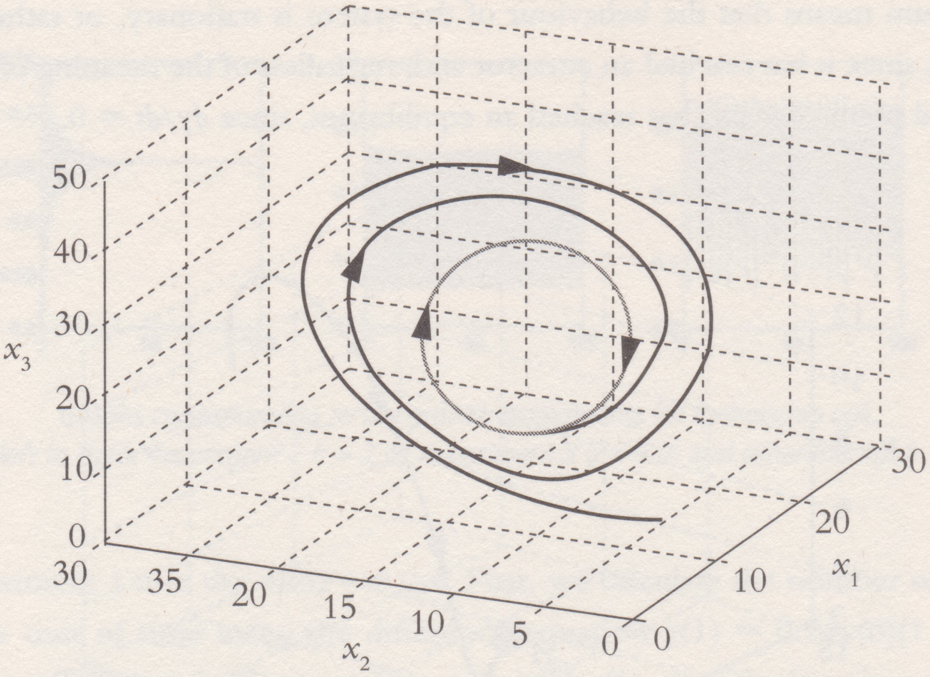
In the experiment, the population reaches what is referred to as a point attractor at $y = 0$. Since $y = 0$, the population has died off, one of the possible states to which a population may evolve in nature. An attractor is nothing more than a point or set of points to which a dynamic system tends, or approaches. In our experiment, it is the orbit formed by the number of bacteria in the population. Consequently, the equilibrium means that the behaviour of the system is stationary, or rather it does not vary, since it has reached an attractor and, regardless of the meaning of y from a biological point of view, has reached an equilibrium, since $dy/dt = 0$.



Point attractor.

In comparison to the first experiment, the population of bacteria in experiment 2 has fared better. The population has also moved towards an equilibrium, but on this occasion it does not die off, since we are dealing with the point attractor $y = 0.6$. In experiment 3, the number of bacteria seems to oscillate between a maximum and minimum value. This means that depending on the time t, if the microbiologist counts the number of bacteria in the receptacle, the final value of the count will vary between a maximum and minimum number. In this case, we also say that the population has reached an equilibrium.

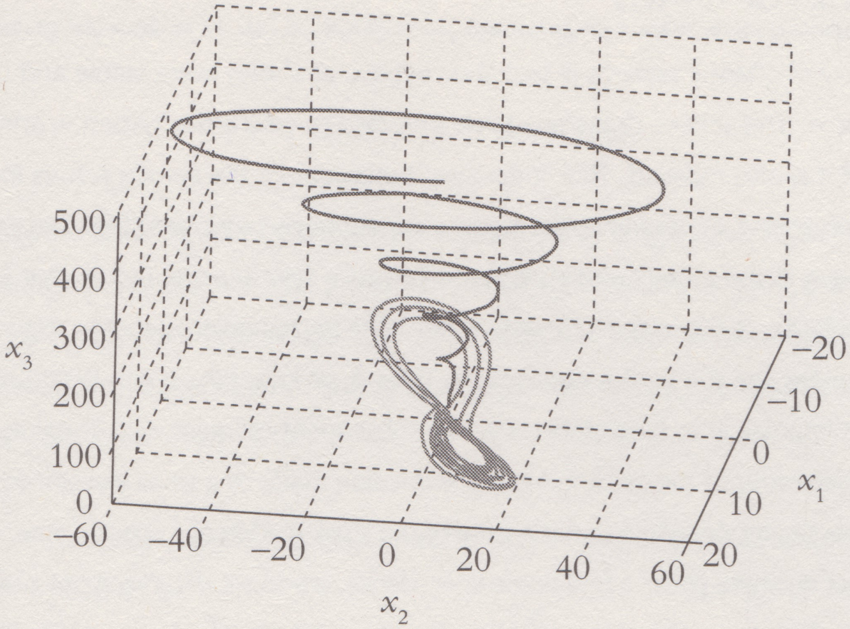
However, this time, given the oscillation between the two extremes, the equilibrium is determined by what is referred to as the limit cycle. In this case, we are dealing with a closed orbit or path, often characteristic of systems whose behaviour oscillates. From a geometric point of view, an attractor acts as a drain, and can be a point, a curve or even a fractal – a concept we shall discuss shortly. Consequently, stable systems, such as the bacterial culture we are studying, are those that tend towards an attractor over time, whereas unstable systems escape from attractors.



Limit cycle.

However, what happens in the last experiment – number 4? We can see immediately that there is no pattern in the oscillation of the curve for this experiment. The oscillations, and hence the population behave in a chaotic fashion. Under these circumstances it is impossible to determine the precise value of the number of bacteria in the population, since the number will vary significantly depending on the time at which they are counted. Furthermore, and this is the crux of the matter, this variation in the number of bacteria does not appear to conform to a pattern, in contrast to what happens in the first three experiments.

Consequently, we can conclude that chaos is the absence of a pattern of oscillation and arises when the system reaches a critical value for the parameter of a differential equation. In the experiment in question, the critical value of the parameter is $r = 3.6$, whereby the population and its orbit of values $y(0)$, $y(1)$, $y(2)$..., $y(100)$, has become trapped by what is known as a strange attractor. The climate of planet Earth, stock market indices and human heart rhythm all naturally exhibit chaotic behaviours, with their dynamism being governed by a strange attractor.



Strange attractor.

Studying the behaviour of nature step by step

In the previous chapter, we discussed how mathematical biology studies biological phenomena and systems using a type of classical expression, differential equations. However, this is not the only procedure available for studying dynamic systems and modelling and simulating a biological phenomenon. Another of the techniques currently used is functions or maps. In fact, the method is simpler than using differential equations. A classic example is the so-called logistical map. Instead of using the Verhulst differential equation $y' = ry(k - y)$ we use the expression

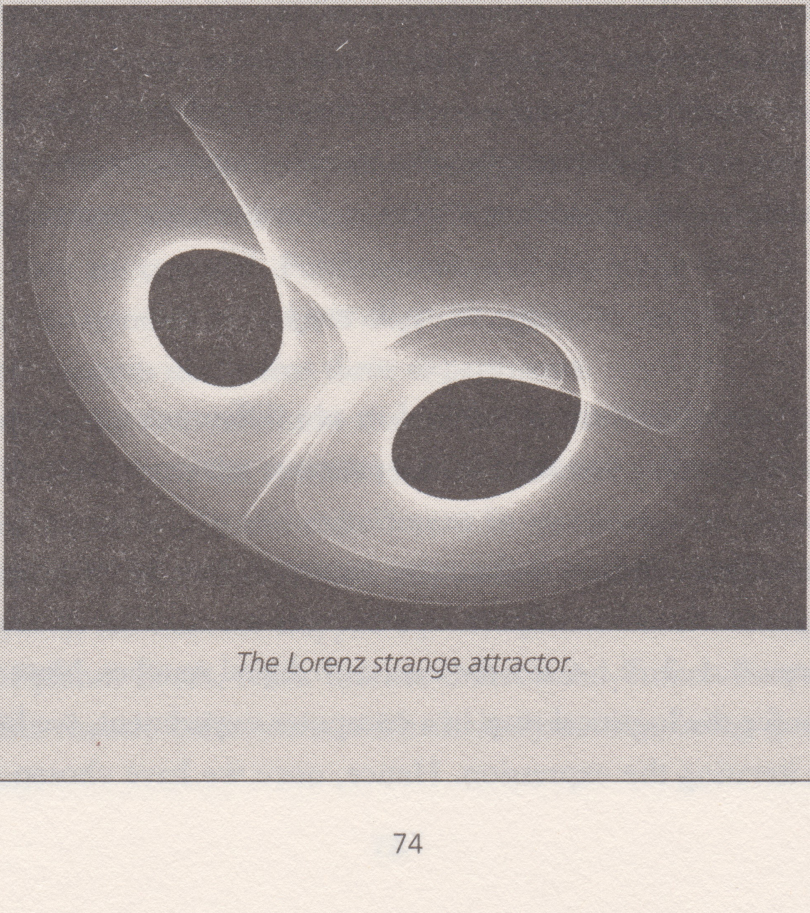
$$y_{n+1} = ry_n(k - y_n),$$

which, on account of its form, is referred to as a difference equation. Remember that this latter expression was used in the previous section to introduce us to the study of chaos.

In differential equations, *n* is the most common way of referring to the time *t*. Now time – and this is an important observation – is discrete, meaning that it increases in steps, 0, 1, 2, 3..., *t*, as is the case with digital watches. Note that if we use the expression for the logistical map in a computer experiment, we limit ourselves to repeatedly iterating the expression. Hence, once we have chosen the values of

PROPERTIES OF CHAOS

One property of chaotic systems is that they behave as if they were stable and unstable at the same time. This means that there is an attractor to which the system is attracted, but from which it is also repelled. This 'indecisive' behaviour of the system results in extremely interesting properties. For example, the systems are extremely sensitive to their initial conditions. Small changes in the initial conditions, even of just a few decimal places due to errors in measurements, cause the forecast for their future state to change dramatically. A good example of this is climate and the Earth's atmosphere. Even if we know the current state of a chaotic system, it is impossible to predict its state at a subsequent moment with certainty, including (sadly) the behaviour of the stock market. The decision made by a small investor to buy or sell some of their shares, depending on the state of the stock market at a specific time, could have a large effect on share prices a few hours later. Hence, paradoxically, in spite of being systems governed by differential equations, chaotic systems exhibit complex behavioural patterns. This behaviour is explained by the existence of a strange attractor. Hence, for example, the Lorenz attractor represents a strange attractor of the simplest possible model of the Earth's climate. Another strange attractor is the Henon attractor, which is related to how the neural networks of a brain memorise a pattern as the connections between neurons (nerve cells). Julia sets are a strange attractor. They are fractals, genuine attractors that explain certain biological shapes such as bacteria and protozoa.



The Lorenz strange attractor.

k, r and the initial number of individuals, such as bacteria, $y(0)$, all we need to do is compute the values of $y(1)$, $y(2)$, $y(3)$, etc., making use of the expression:

$$y\,(t + 1) = r\star y(t)\star(k - y(t)),$$

where $\star$ is the product operator used in programming languages. It is standard practice for mathematicians to say that given the starting conditions $y(0)$, the sequence of values $y(1)$, $y(2)$, $y(3)$, etc. represents the orbit of point $y(0)$. With a basic knowledge of programming, and regardless of the language used, we can see that the programme is reduced to the following code:

```
starting conditions and parameters of the logistical map:
y(0): r: k
maximum simulation time:
tmax
Difference equation:
For t = 0 TO tmax
$y(t + 1) = r\star y(t)\star(k - y(t))$
print t, y(t + 1)
End
```

The difference between this method and using differential equations is that integration is substituted for iteration. In other words, the calculation of an integral is not required, and instead we repeat the same mathematical operations over and over again.

This idea of repeated calculations leads to the concept of mapping, a term commonly used by specialists. Hence, for example, the ecologist maps the future state of a system $y(t + 1)$, such as a lake or meadow, based on its current state $y(t)$. If the process is repeated over and over again, it is possible to predict the evolution of the lake or meadow.

Let us take this a step further. What would the previous programme look like, if instead of using the logistical map, the Verhulst equation was used on the computer? In this case we would not only have to make use of iteration but also of integration, as described in the previous chapter.

There are different methods for tackling the integration of a differential equation. Not only are these methods common in ecology, physiology and pharmacology, but they are also widely used in many other disciplines, such as economics, as well as areas as diverse as political sciences and chemical engineering.

These methods of integrating differential equations using a computer are known as numerical integration methods. The simplest and most popular method is Euler's method, or the tangent method, although in practice one of the most precise is the fourth-order Runge–Kutta method. Applying any of these methods will give approximate values of $y(1)$, $y(2)$, $y(3)$, etc., although for the values to be exact, we would need to integrate the differential equation 'by hand' and repeatedly substitute them in the expansion of the solution to the value t equal to 1, 2, 3 etc. Let us assume that we apply Euler's method, in which case the program for simulating the Verhulst differential equation will be:

```
starting conditions and parameters for the Verhulst equation:
y(0): r: k
maximum simulation time:
tmax
Time increment:
Inct
Differential equation:
For t = 0 TO tmax
y(t + 1) = y(t) + Inct*( r*y(t)*(k − y(t)) )
print t, y(t + 1)
End
```

It is immediately clear that solving a differential equation using a computer and applying Euler's method entails predicting the future state of the system $y(t+1)$ based on the initial state $y(t)$, as if we were carrying out iterations using a difference equation. However, there is one point to note. We include the product of the time that has elapsed between $y(t+1)$ and $y(t)$ in the final computation as a result of the differential equation.

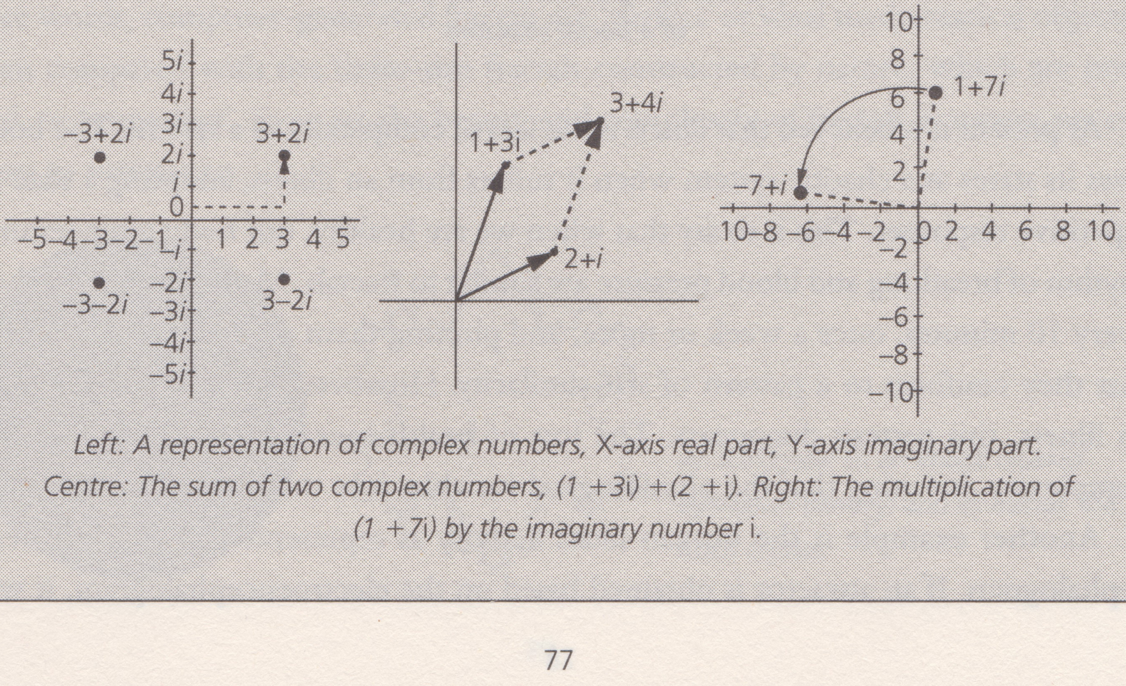
It can be shown that Euler's equation is nothing more than the equation for a straight line, the gradient of which is given by the differential equation. Using the line tangent to a point it is possible to predict the future state or behaviour $y(t+1)$ of the system with greater precision than using the difference equation.

In addition to differential equations and the use of functions or maps, there is a third modelling and simulation technique for dynamic systems known as cellular automata.

THE MAGIC OF COMPLEX NUMBERS

Since ancient times, human beings have felt an irresistible urge to transgress their own limitations. This tendency has made possible all sorts of interventions. However, if there is one area in which human beings have been especially creative, it is mathematics. Complex numbers are just one example of this. The questions of whether there exists a number that has a negative square and if square roots of negative numbers were possible received an affirmative answer from the two Italian mathematicians Girolamo Cardano and Rafael Bombelli in the second half of the 16th century. Such numbers were given the rather poetic name of imaginary numbers. From then on, the imaginary unit has been conventionally represented using the letter i whose value is $i = \sqrt{-1}$ or, alternatively, $i^2 = -1$.

Complex numbers are based on the imaginary unit. While in everyday life we are used to numbers such as 10.23, 6, 1/2, etc., the practitioners of various fields of science and technology are used to making use of complex numbers. They consist of two parts – a real part a and an imaginary part b. Examples of complex numbers include $3 + 2i$, $6 + 7i$, etc., and they take the form $a + bi$, which is how these numbers are written. However, note that a and b are real numbers. What is genuinely surprising is that complex numbers have an infinite number of applications in biology, engineering, applied mathematics, etc. These fascinating numbers and the operations that can be carried out with them are considered in greater detail in the appendix to this book.

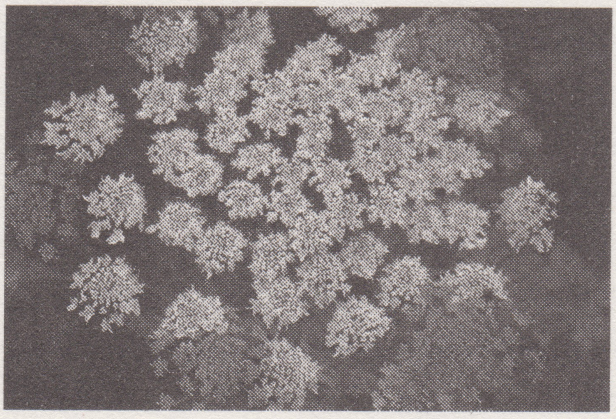


Left: A representation of complex numbers, X-axis real part, Y-axis imaginary part. Centre: The sum of two complex numbers, $(1 + 3i) + (2 + i)$. Right: The multiplication of $(1 + 7i)$ by the imaginary number i.

Is nature fractal?

Nature constructs inanimate objects (such as clouds, mountains, coasts, ice crystals, etc.), living things (such as plants, microorganisms, algae, coral, etc.) and structures (such as the bronchial system, the vascular system and the branching of neurons) by applying a simple procedure – repeating a pattern over and over. Regardless of the level at which the observation is carried out, we will find that there is a pattern that is repeated, whether we are observing it on a scale of metres, centimetres or even millimetres. These self-similar structures are referred to as fractals.

The idea is simple – nature builds structures by applying a criterion of economy. It creates a pattern or 'architectonic design' and repeats this at different scales inside and outside the object. A classical example, which has long attracted the attention of botanists, is the branching system of plants. Hence, for example, it is easy to see how the organisation of a branch is, together with the smaller branches it contains, a repeated version of the plant as a whole.



The branching of plants is an example of a fractal structure.

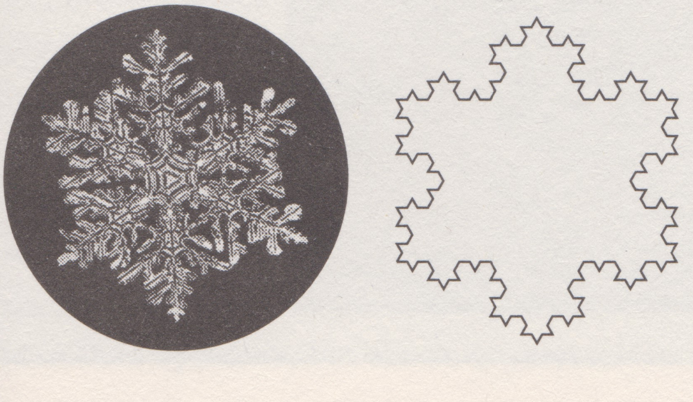
At present it is believed that illness is the loss of complexity in a system. The body loses its status as a chaotic system when it suffers from an illness, adopting a state of repetitive responses. This is to say that when we are healthy, our body temperature, rhythm of breathing and blood pressure are similar to fractals. Measuring their values every 10 minutes, once a week or more, and plotting them on a graph, we can see that they conform to a pattern of self-similarity. However, when we suffer from an illness, this pattern disappears. The loss of health causes the body to lose this complexity, meaning that the physiological variables lose their fractal behaviour.

Another example is the human heart activity as represented in an electroencephalogram. If an attractor is obtained based on the electroencephalogram, it will be fractal in nature. Calculating its dimension *D*, which we shall discuss shortly, gives a numeric value. What is most interesting from a neurophysiological point of view is that the value *D* depends on the state of the subject and varies depending on whether we are dealing with a healthy person who is awake, a healthy person under the effects of anaesthetic or a person suffering from epilepsy.

However, what are the properties of fractals that make them so interesting? First of all, their dimension is not a whole number. In our world, referred to as Euclidean by mathematicians, we are used to dealing with whole-number dimensions. For example, a sheet of paper has a length and width, making its dimension, *D*, 2. If we draw a straight line on the paper using a ruler, its dimension *D* is 1. The room in which there is a table on which we have placed the sheet of paper on which we have drawn the straight line has a length, width and height. This means that the room has three dimensions, or $D = 3$. Saying that fractals have a dimension that is not a whole number means that the value of their dimension *D* is 1.8, 2.6 or a number of a similar nature.

Furthermore, fractals are infinite, meaning that, regardless of the level at which we observe them, the structures appear inexhaustible. This is one of the classical experiments that can be carried out using computer programs such as Fractint or Ultra Fractal. If we zoom into a region of the fractal, it is always possible to go further, all the way to infinity. Furthermore, by carrying out this experiment, we can see that fractals are self-similar. In other words, we feel as if we are seeing the same pattern all the time, a pattern that perpetually reveals itself in all its beauty and complexity, but without changing, regardless of the level of observation.

These properties are present in all fractals constructed by mathematicians. In other words, computer-generated fractals are 'perfect' or ideal mathematical objects when compared with the finite-size fractals constructed by nature, which are not ideal, or 'imperfect'. Even so, the beauty and complexity of fractals in nature never ceases to surprise us.



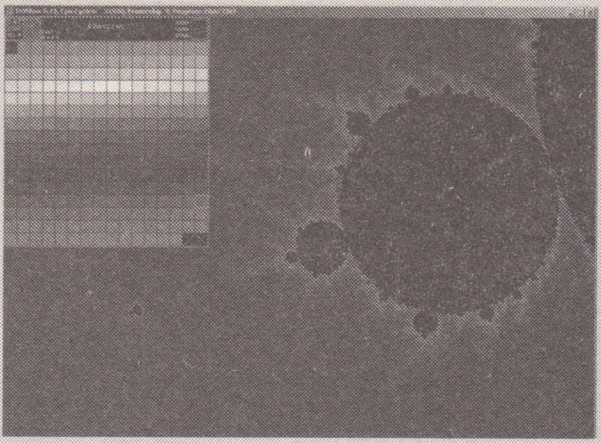
An ice crystal (in an image created by Wilson Bentley) and its fractal, the Koch crystal.

DRAWING FRACTALS ON A COMPUTER

One of the classic programs used for drawing fractals on a computer is FractInt, with versions available for Windows, Linux and Mac Os. One of its most attractive features is its powerful zoom, which can be used to navigate the insides of a fractal with a precision of up to 1,600 decimal places. It is arguably one of the best programs due to the power of its algorithms and its high mathematical precision.

Another feature that must be considered when dealing with this type of program is their utilities. For example, Ultra Fractal allows users to create fractals that change colour, use layers and masks, make animations, etc. The use of layers makes it possible to draw a fractal on different layers and then combine them to produce fascinating effects. Despite being oriented towards the design of fractals with a 'nebulous' appearance, Aphysis is another leading tool. The program, developed by Mark Townsend, makes it possible to create this type of fractal and its variants by simulating mutations on a previously defined fractal.

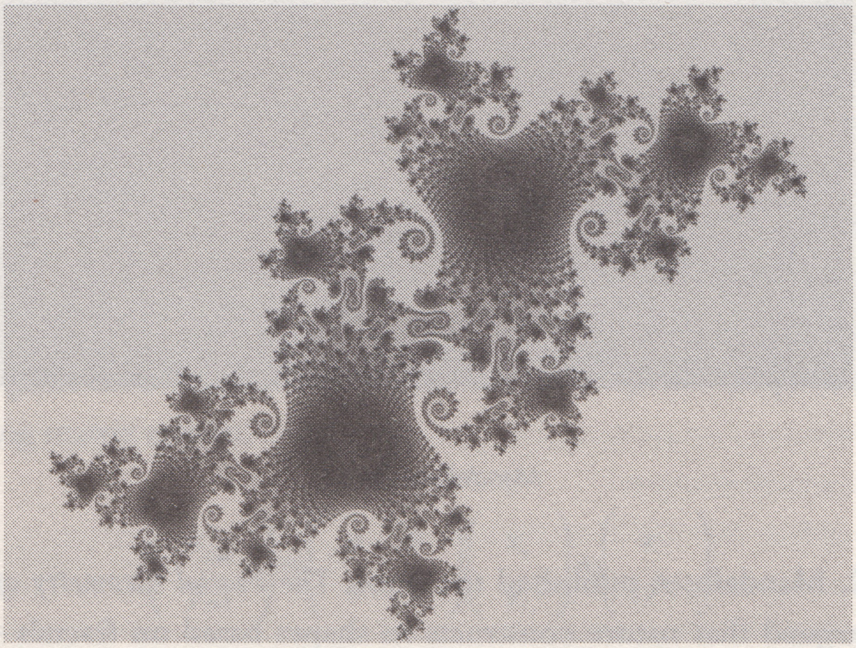
Within the range of available programs, there are a few that stand out on account of the number of options they offer. For example, Fractal Explorer boasts 148 types of fractals and allows users to create strange attractors (3D attractors). It also includes iterative function systems and up to 22 classes of what are known as quaternions. Furthermore, it allows users to create special effects using 117 filters, has 12 colour algorithms and offers the possibility of creating animations in AVI format, etc. One of the most interesting aspects of the program is FEParser (© Kyle McCord), a compiler for formulae designed for advanced users who wish to experiment with their own fractals. Other programs, such as XenoDream, stand out on account of their artistic features, with options to add textures and lighting, create 3D fractals and even animations and stereograms. These programs represent just some examples of the wide range available to suit all needs, from simply enjoying the image to the mathematical study of these objects or the creation of computer-based art.



An image generated by Fractint.

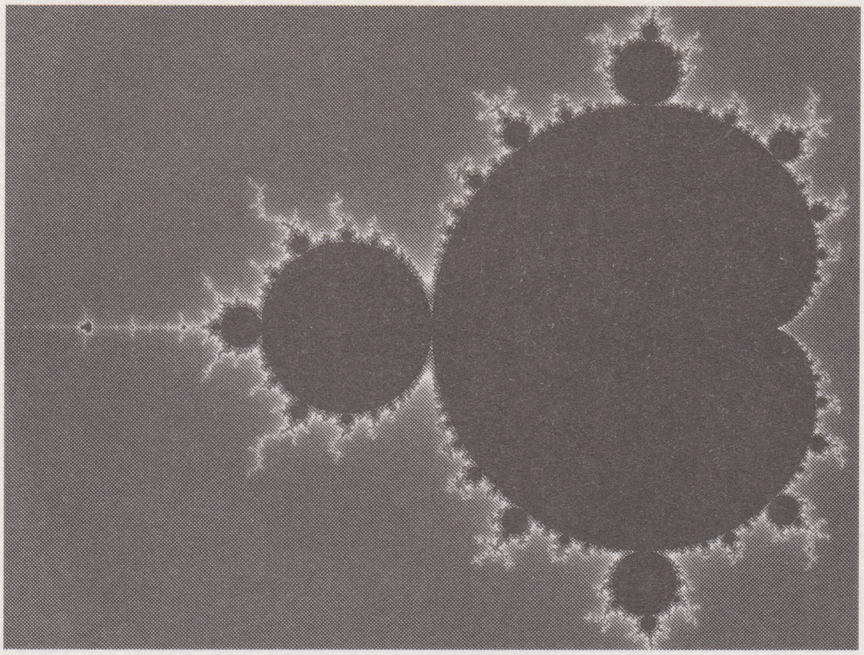
The Julia and Mandelbrot sets

Gaston Julia was a French mathematician and a pioneer in the study of fractals. In spite of the importance of his discoveries, he died in 1978 without achieving much fame. One of the reasons for this was that the computers of the time did not have the graphical capabilities they have today, which allows them to represent fractal objects in all their beauty and apparent complexity. Furthermore, anecdotally, Julia was unlucky, since a wound to his face caused during World War I required him to keep it partially covered throughout his life.



Julia set fractal.

Imagine a function of the form $Z_{n+1} = Z_n^2 + C$, where Z is a variable and C a constant. In this expression, the value of the term on the left of the iteration $n + 1$ is equal to the square of Z in the previous iteration n plus the value of the constant C. At first glance, the expression seems of little interest, except when the variable Z and the constant C are complex numbers. This was precisely the case studied by Julia. Years later, Benoit Mandelbrot also studied this type of iterative expression with the help of a computer. In a certain sense, Mandelbrot continued the work started by Gaston Julia on fractals, and has made one of the greatest contributions to the popularity of this type of object. In 1958 he joined an IBM research centre in the United States and studied not just the use of fractals as applied to physics, such as in fluid dynamics, but also in economics. In 1975, he coined the term *fractal* to describe this type of object and, studying the Julia set on a computer, discovered the set that bears his name, the Mandelbrot set.



Mandelbrot fractal.

In 1982, Mandelbrot published the book *The Fractal Geometry of Nature*, in which he argued that nature constructs its shapes based on fractals – as can be seen in coastlines, mountains, plants, and blood vessels and lungs. However, what is the difference between the two types of fractals? Mandelbrot sets study what is known as orbit 0. Mandelbrot proposed studying the repeated iteration of the expression $Z_{n+1} = Z_n^2 + C$ for the specific case when Z_0 is 0. The idea was to observe the set of values of C under these conditions for which the resulting orbit did not escape to infinity.

This specific set of values was given the name the Mandelbrot set. In contrast, Julia sets assign the complex constant C a fixed value and study the behaviour of the function, its orbit, and hence, Z_0, Z_1, Z_2,..., etc. Since computers cannot work with complex numbers, both the variable and the constant can be written as follows:

$$Z = X + iY$$
$$C = p + iq,$$

breaking the function $Z_{n+1} = Z_n^2 + C$ down into its real X and imaginary Y parts. We can now use a computer to represent the points of the orbit on the Argand plane, a Cartesian system X-Y, that represents the points for $\sqrt{X^2 + Y^2}$ below a pre-defined value and not escaping to infinity. This orbit does not escape to infinity, but the border at which the points do escape to infinity is referred to as the Julia set.

Barnsley's chaos game

Chaotic systems are a class of dynamic systems. Michael F. Barnsley at the Georgia Institute of Technology explained them to his students using what he called the 'chaos game'. What Barnsley was trying to show was not how a chaotic system behaved dynamically, but that the peculiarity of what appeared disordered was only peculiar in appearance and that the same shape was always obtained. This shape was clearly an attractor, specifically a fractal, although it remained unrecognisable until the simulation experiment had reached an advanced stage. Remember that an attractor is nothing more than the point or set of points to which a dynamic system tends. The game involves graphically representing the points (x, y) obtained using the following matrix system:

$$\begin{pmatrix} x_{t+1} \\ y_{t+1} \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} x_t \\ y_t \end{pmatrix} + \begin{pmatrix} e \\ f \end{pmatrix}$$

To begin with, we obtain a cloud of points arranged in an apparently random fashion. However, towards the end of the experiment, once enough points have been plotted, we always obtain a strange attractor, known as the Sierpinski triangle.

Barnsley's idea was simple, elegant and spectacular. Any point we draw in the future, indicated as $t + 1$, will have coordinates (x_{t+1}, y_{t+1}), which will always be obtained from the point we have just represented graphically at time t, with coordinates (x_t, y_t). Note that this mapping recalls the experiment with the logistical map or Verhulst equation. We shall discuss matrices and their application in mathematical biology in the following chapter. However, for now let us note that the above expression yields another two more conventional expressions, giving the coordinates of the new point based on the following transformations:

$$x_{t+1} = ax_t + by_t + e,$$

$$y_{t+1} = cx_t + dy_t + f.$$

The experiment carried out by Barnsley in the 'chaos game' consists of defining three sets of transformations, referred to as:

Set 1	Set 2	Set 3
$x_{t+1} = 0.5x_t + 1$ $y_{t+1} = 0.5y_t + 1$	$x_{t+1} = 0.5x_t + 50$ $y_{t+1} = 0.5y_t + 1$	$x_{t+1} = 0.5x_t + 1$ $y_{t+1} = 0.5y_t + 50$

Given an arbitrary starting point (x_t, y_t), a number 1, 2 or 3 is obtained by a random method, such as throwing a die. If a 1 or 2 is obtained, set 1 is chosen; if a 3 or 4 is obtained, set 2 is chosen; and if a 5 or 6 is obtained, set 3 is chosen. Having chosen a new set of equations, the new point (x_{t+1}, y_{t+1}) is obtained based on the previous point, representing it graphically. We then draw a new set of transformations, transforming the previous point and obtaining another, and so on.

Note that in the experiment that leads to the Sierpinski triangle, a and d are always 0.5, while b and c are 0. The values of e and f vary for each transformation. Other fractals that represent biological shapes, such as the leaves of plants, ferns, etc. can be obtained by applying this procedure with different values of a, b, c, d, e, and f for the transformations.

The procedure that has been described, one of the most important for creating fractals on a computer, is referred to as iterative function systems. The conclusion is surprising. Many biological structures and shapes are fractals. If, for example, the points represented by cells are subject to what mathematicians call transformations (rotations, shifts, changes of scale), we obtain a final structure that is a fractal, such as the leaf of a plant.

Chapter 4

Playing Sudoku with Life

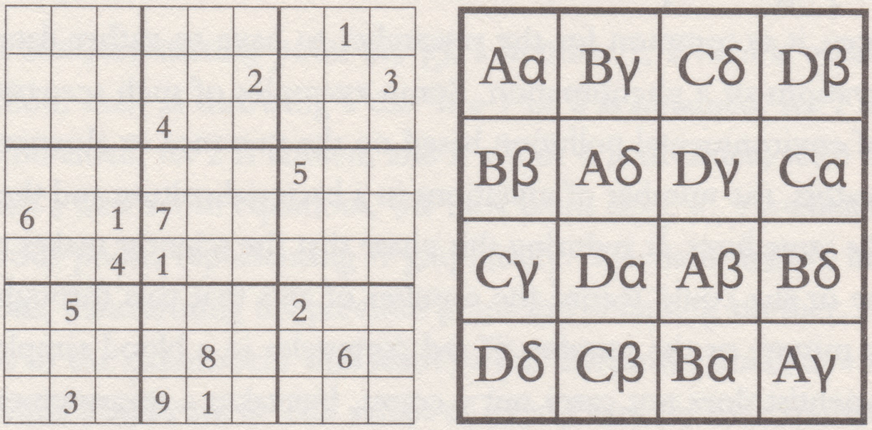
One of the most common tasks carried out by scientists is the observation of nature and carrying out experiments in the field or in the laboratory. Under these circumstances, it is common for the researcher to have to gather data as part of their observations of a phenomenon. Some examples of such scenarios include the study of environmental pollution based on the presence or absence of certain lichen indicators, the number of mutations in a bacterial culture and the weight of rats from the same litter. It is during this phase that the scientist makes counts. For example, he or she could record the number of ants that pass through a specific place every minute or the number of red corpuscles in a blood sample. In other cases, the scientist does not carry out a count, but takes a measurement. Hence, they can measure the acidity of a substance by its pH, or its weight, height or any other physiological measurement.

Tables, sudoku and matrices

Once the data has been collected, the values are organised in tables. Let's assume that a greenhouse has seven varieties of plants in batches of four and each plant in the batch is given a different fertiliser; hence, there are four possible fertilisers. After a certain period of time the number of leaves is counted on each plant to see if any type of fertiliser increases the number of leaves. Let x be the number of leaves, regardless of the value. The standard format of these tables is shown below:

	1	2	3	4
1	x_{11}	x_{12}	x_{13}	x_{14}
2	x_{21}	x_{22}	x_{23}	x_{24}
3	x_{31}	x_{32}	x_{33}	x_{34}
4	x_{41}	x_{42}	x_{43}	x_{44}
5	x_{51}	x_{52}	x_{53}	x_{54}
6	x_{61}	x_{62}	x_{63}	x_{64}
7	x_{71}	x_{72}	x_{73}	x_{74}

Hence, for example, x_{23} represents the number of leaves on plant 2 with fertiliser 3, and x_{74} represents the number of leaves on plant 7 with fertiliser 4. Experiments of this nature have been studied by mathematicians since long ago, due to their significance in agricultural production. The traditional technique is to use the concept of the Latin square. A particular type of Latin square that is currently extremely popular is the game of sudoku.



							1	
					2			3
			4					
						5		
6		1	7					
		4	1					
	5					2		
				8			6	
	3		9	1				

Aα	Bγ	Cδ	Dβ
Bβ	Aδ	Dγ	Cα
Cγ	Dα	Aβ	Bδ
Dδ	Cβ	Bα	Aγ

An example of sudoku, a popular Japanese pastime (left), and a Latin square (right). They are tables or matrices in which one symbol, such as a number, or the combination of two or more symbols, only appears once in each row and column.

Let us now consider a general definition of the table defined in the experiment with the plants and fertilisers. In this case, in mathematical notation we can say there are m plants and n types of fertilisers, rewriting the previous table between two large brackets:

$$\begin{pmatrix} x_{11} & x_{12} & x_{13} & \cdots & x_{1n} \\ x_{21} & x_{22} & x_{23} & \cdots & x_{2n} \\ x_{31} & x_{32} & x_{33} & \cdots & x_{3n} \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ x_{m1} & x_{m2} & x_{m3} & \cdots & x_{mn} \end{pmatrix}$$

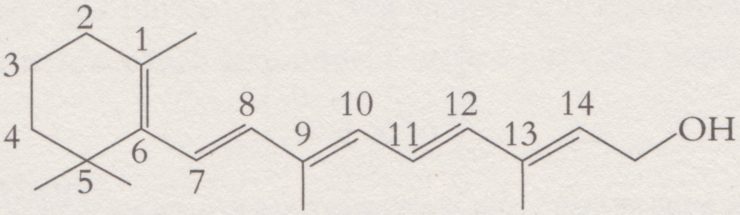
This way of presenting the data is called a matrix. Hence, an $m \times n$ matrix is simply a set of $m \times n$ elements organised into m rows and n columns. Matrices are often represented using capital letters: A, B, C, etc. Their importance stems from the fact that they do not just make it possible to organise data, but also to represent systems of equations. For example, consider the systems of linear equations shown below:

$$\begin{cases} 3x+2y=7 \\ 5x-y=4. \end{cases}$$

Using matrix notation, the system of equations can be represented as:

$$\begin{pmatrix} 3 & 2 \\ 5 & -1 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix}=\begin{pmatrix} 7 \\ 4 \end{pmatrix},$$

Furthermore, matrices can be used to analyse the chemical structure of a molecule. For example, if we arbitrarily label the C atoms of vitamin A or retinol, as shown below:



the following matrix represents the vitamin A molecule:

$$\begin{pmatrix}
0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0
\end{pmatrix}$$

MATRICES: VARIETY IS THE SPICE OF LIFE

It is common to come up against the special terminology used for matrices. Here we provide definitions of some of the most commonly used terms.

Square Matrix, has the same number of rows *m* and columns *n*:

$$\begin{pmatrix} 2 & 3 & -1 \\ 5 & 2 & 8 \\ 9 & 7 & 6 \end{pmatrix}$$

Symmetric Matrix, a square matrix in which $x_{ij} = x_{ji}$:

$$\begin{pmatrix} 3 & 1 & 5 \\ 1 & 2 & -4 \\ 5 & -4 & 0 \end{pmatrix}$$

Unit or Identity Matrix, a square matrix with all elements equal to 0, except those of the main diagonal, which are 1; often written as I:

$$\begin{pmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \cdots & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

Diagonal Matrix, a square matrix with all elements equal to 0, except those of the main diagonal:

$$\begin{pmatrix} 2 & 0 & \cdots & 0 \\ 0 & -1 & \cdots & 0 \\ \vdots & \vdots & \cdots & 0 \\ 0 & 0 & 0 & 5 \end{pmatrix}$$

Zero Matrix, a matrix that is not necessarily square, with all its elements equal to 0; often written as 0:

$$\begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

Triangular Matrix, square matrix in which the elements located above or below the main diagonal are zero. The matrix on the left is an example of an upper triangular matrix, whereas the one on the right is a lower triangular matrix.

$$\begin{pmatrix} 8 & 3 & -2 \\ 0 & -5 & 9 \\ 0 & 0 & 1 \end{pmatrix}\begin{pmatrix} 2 & 0 & 0 \\ -1 & 4 & 0 \\ 5 & 6 & 7 \end{pmatrix}$$

Note that all we have done is to assign the value $x_{ij} = 1$ if two atoms i, j are joined together, and 0 if they do not share a bond.

The relationship between elements can be represented using a graph. The elements of a neural circuit or cellular metabolism, for example, can be represented by nodes that are connected by arcs. This makes it possible to associate a matrix with a graph, as we did for A.

Matrices are extremely interesting since they allow us to represent experimental data, systems of equations and graphs. However, what is also extremely important is the fact that we can carry out operations on matrices. Since the second half of the 19th century, we have known how to carry out operations on data organised in rows and columns, such as matrix addition and multiplication. This means that we know the rules to be followed for carrying out these operations, giving us what is known as matrix algebra, which forms the basis of many quantitative techniques in mathematical biology and other disciplines. Examples would be the study of dynamic systems in ecology and physiology, or the analysis and resolution of numerous situations from genetics, which are normally carried out using matrix operations.

Matrix operations

In this section we shall describe some of the most commonly used matrix operations. Understanding these operations will allow us to understand an endless number of applications.

Addition

One of the most basic matrix operations is addition. Imagine that in an experiment, a biologist has two 2×2 matrices, A and B:

$$A = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}, B = \begin{pmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{pmatrix}$$

such that:

$$A = \begin{pmatrix} 2 & 4 \\ 0 & -1 \end{pmatrix}, B = \begin{pmatrix} 5 & -6 \\ 3 & 1 \end{pmatrix}$$

What is the matrix C given by the sum $A + B$? The elements of the matrix C are $c_{11} = a_{11} + b_{11}$, $c_{12} = a_{12} + b_{12}$, $c_{21} = a_{21} + b_{21}$ and $c_{22} = a_{22} + b_{22}$:

$$C = \begin{pmatrix} c_{11} & c_{12} \\ c_{21} & c_{22} \end{pmatrix} = \begin{pmatrix} 7 & -2 \\ 3 & 0 \end{pmatrix}$$

Note here that the number of columns in A must be equal to the number of rows in B. For example, imagine a laboratory for the treatment of human fertility that uses a model that labels an ovule or spermatozoid carrying a dominant A with 1, and 0 if the gene is recessive. If a spermatozoid fertilises an egg, the following sum will give all the possible embryos for the gene in question:

$$\begin{pmatrix} 1 & 1 \\ 0 & 0 \end{pmatrix} + \begin{pmatrix} 1 & 0 \\ 1 & 0 \end{pmatrix} = \begin{pmatrix} 2 & 1 \\ 1 & 0 \end{pmatrix}$$

In our example, 2, 1 and 0 represent embryos AA, Aa and aa respectively.

Subtraction

The matrix subtraction $A - B$ is similar to summation, with the result being given by $A + (-1)B$. To subtract the matrices A and B from the first example:

$$\begin{pmatrix} 2 & 4 \\ 0 & -1 \end{pmatrix} - \begin{pmatrix} 5 & -6 \\ 3 & 1 \end{pmatrix}$$

we must first change the sign of the elements of B:

$$\begin{pmatrix} -5 & 6 \\ -3 & -1 \end{pmatrix}$$

and then add the resulting matrix to A, giving the subtraction of the two matrices:

$$\begin{pmatrix} -3 & 10 \\ -3 & -2 \end{pmatrix}$$

Multiplication

Another basic matrix operation is the product of a number and a matrix. Let k be an arbitrary number, such as a constant or even a function $y(x)$, referred to by mathematicians as a scaler, and A, a matrix.
The product or multiplication $k \cdot A$:

$$k\begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$$

is equal to

$$\begin{pmatrix} k\cdot a_{11} & k\cdot a_{12} \\ k\cdot a_{21} & k\cdot a_{22} \end{pmatrix}$$

For example, imagine that in soil that has suffered deterioration from previous cultivation, an experiment is carried out on the effects of four types of fertilisers, in which the proportions of nitrogen, phosphorus and potassium vary. Fertilising four plots of land with each of the fertilisers, we find that in the first, 5% of seeds germinate; in the second, 15%; in the third, 8%; and in the fourth, 27%. If 80 seeds are sown in each plot, using a_{11}, a_{12}, a_{21}, and a_{22} for the first, second, third and fourth plots, the number of seeds that germinate in each will be equal to:

$$80\begin{pmatrix} 0.05 & 0.15 \\ 0.08 & 0.27 \end{pmatrix} = \begin{pmatrix} 4 & 12 \\ 6 & 22 \end{pmatrix}$$

The product or multiplication of matrices is one of the most common applications in mathematical biology and other disciplines. The precondition for the multiplication of two matrices A_{mxn} and B_{nxp} is that the number of columns n of A is equal to the number of rows n of B, making the product of $A \cdot B$ a matrix C_{mxp} with m rows and p columns. Let use the standard mathematical notation to write this operation, which we shall then illustrate by means of an example.

Given two matrices A and B:

$$A = \begin{pmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{m1} & a_{m2} & \cdots & a_{mn} \end{pmatrix}, \ B = \begin{pmatrix} b_{11} & b_{12} & \cdots & b_{1p} \\ b_{21} & b_{22} & \cdots & b_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ b_{n1} & b_{n2} & \cdots & b_{np} \end{pmatrix}$$

their product is equal to the matrix C:

$$C = \begin{pmatrix} c_{11} & c_{12} & \cdots & c_{1p} \\ c_{21} & c_{22} & \cdots & c_{2p} \\ \vdots & \vdots & \cdots & \vdots \\ c_{m1} & c_{m2} & \cdots & c_{mp} \end{pmatrix}$$

In the matrix C the general element c_{ij} is given by the following expression:

$$a_{i1}b_{1j} + a_{i2}b_{2j} + \ldots + a_{in}b_{nj}.$$

To determine the element c_{11} we must take the elements $a_{11}, a_{12}\ldots, b_{11}, b_{21}\ldots$, and use them to calculate $a_{11}\,b_{11} + a_{12}b_{21} + \ldots + a_{1n}\,b_{n1}$.

However, it is perhaps easier to illustrate the product of two matrices by means of a practical example. Imagine two matrices A and B:

$$A = \begin{pmatrix} 3 & 2 & 1 \\ 0 & -1 & 6 \\ 7 & 4 & 5 \end{pmatrix}, \ B = \begin{pmatrix} 2 & 0 \\ 6 & 1 \\ -3 & 4 \end{pmatrix}$$

If we carry out the product $A \cdot B$ in line with the following operations:

$$\begin{pmatrix} (3)\cdot(2)+(2)\cdot(6)+(1)\cdot(-3) & (3)\cdot(0)+(2)\cdot(1)+(1)\cdot(4) \\ (0)\cdot(2)+(-1)\cdot(6)+(6)\cdot(-3) & (0)\cdot(0)+(-1)\cdot(1)+(6)\cdot(4) \\ (7)\cdot(2)+(4)\cdot(6)+(5)\cdot(-3) & (7)\cdot(0)+(4)\cdot(1)+(5)\cdot(4) \end{pmatrix}$$

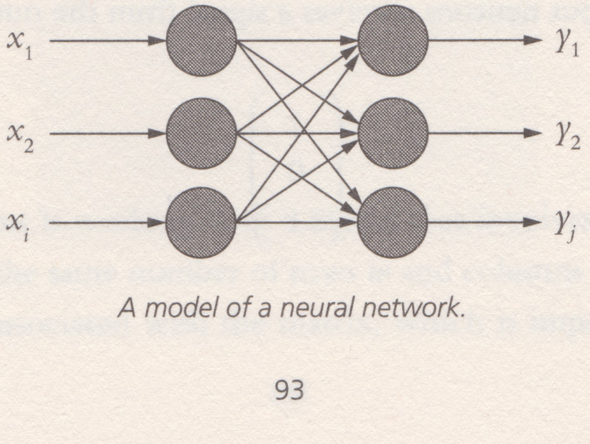
the result is the matrix:

$$\begin{pmatrix} 15 & 6 \\ -24 & 23 \\ 23 & 24 \end{pmatrix}$$

It is important to bear in mind that for the sum of two matrices $A + B$, the result of calculating $A + B$ and $B + A$ is the same. That means addition is commutative, but the same cannot be said for multiplication, which is a non-commutative operation. For matrix multiplication $A \cdot B$ is not the same as $B \cdot A$. Keeping in mind this property, one of the most interesting operations is the product of a matrix A by a matrix B, where B has just one column. Hence, the product $A_{mxn} \cdot B_{nx1}$. This single-column matrix is referred to as a column vector. We shall return to column vectors later to see their applications in biology.

Application of the product of a matrix and a vector

To illustrate an application of the product of a matrix and a vector, imagine a neuroscientist has designed a model of a neural network. In the circuit, a group of neurons represented by circles, referred to as afferent or sensory neurons, are responsible for receiving impulses from the outside world, for example through sensory organs. The afferent neurons send nerve signals to other neurons, the efferent or motor neurons, through their connections or synapses. The purpose of the efferent neurons is to transmit the response to a certain input signal arriving via afferent neurons. These outputs are sent to muscles, a gland, etc. Let us use the input signal that reaches the afferent neurons through the vector $\vec{u}$, the elements of which are those of the column vector x_1, x_2..., x_i to represent the properties of a certain object. Let us use y_1, y_2..., y_j to represent the components of a vector $\vec{v}$ that represents the response sent by the efferent neurons once the input signal has been processed by the neural network.



A model of a neural network.

Finally, let us represent the connections or synapses of the afferent and efferent neurons of the neural network using a matrix *M*. We'll call this matrix the memory matrix, adopting some biological terminology. The elements of the matrix c_{ij} represent the connection or synapse between an input, or afferent neuron *i* and an output or efferent neuron *j*. Summarising what we know about the neural network, a model of its operation can be represented using matrix algebra.

$$\begin{pmatrix} c_{11} & c_{12} & \cdots & c_{1j} \\ c_{21} & c_{22} & \cdots & c_{2j} \\ \vdots & \vdots & \cdots & \vdots \\ c_{m1} & c_{m2} & \cdots & c_{mj} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_i \end{pmatrix} = \begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_j \end{pmatrix}$$

If a neuroscientist who uses this model in their work wants to know the answer for efferent neuron 2, given the remainder of the values, they simply calculate:

$$y_2 = c_{21}x_1 + c_{22}x_2 + \ldots + c_{2j}x_i.$$

And if they want to know the output of the first efferent neuron? It suffices to calculate $y_1 = c_{11}x_1 + c_{12}x_2 + \ldots + c_{1j}x_i$.

To make things clearer, let us consider the following example. Imagine a neural network with three input or afferent neurons, and three output or efferent neurons, where *M* is the matrix of connections or synapses between the neurons of the neural network shown below:

$$\begin{pmatrix} 0.2 & 0.6 & 0.8 \\ 0.3 & 0.9 & 0.4 \\ 0.1 & 0.2 & 0.3 \end{pmatrix}$$

If the layer of input neurons receives a signal from the outside:

$$\begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix}$$

what will be the output of the first efferent neuron? Using the model described opposite:

$$\begin{pmatrix} 0.2 & 0.6 & 0.8 \\ 0.3 & 0.9 & 0.4 \\ 0.1 & 0.2 & 0.3 \end{pmatrix}\begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix}=\begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix}$$

the requested output is $y_1 = (0.2)(1) + (0.6)(0) + (0.8)(1)$ and hence, $y_1 = 1$.

At present, this type of mathematical model is used for pattern recognition for letters, numbers, photographs, etc. in systems equipped with artificial intelligence by engineers using this method.

Obtaining the transpose of a matrix

Another common matrix operation is the transpose. The operation is as simple as switching rows for columns, hence giving the transpose A^t of matrix A. For example, given the matrix A:

$$A=\begin{pmatrix} 6 & 7 & -1 \\ 0 & 1 & 2 \\ -7 & 4 & 3 \end{pmatrix}$$

the transpose A^t is the matrix:

$$\begin{pmatrix} 6 & 0 & -7 \\ 7 & 1 & 4 \\ -1 & 2 & 3 \end{pmatrix}$$

The operation is immediate. Furthermore, calculating the transpose of the transpose, or rather $(A^t)^t$, gives the matrix A. We shall see the usefulness of this operation further on.

Determinants

Imagine that a scientist is working with a model that involves a square matrix, or rather a matrix with the same number of rows m and columns n. In this case, there is a special number associated with the matrix, which is important as it provides us information about certain properties of the matrix. This number is obtained by calculating what is known as the determinant of a matrix. For example, and in the simplest case of a 2×2 matrix, or rather one with two rows and two columns, and whose elements are represented by a, b, c and d:

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

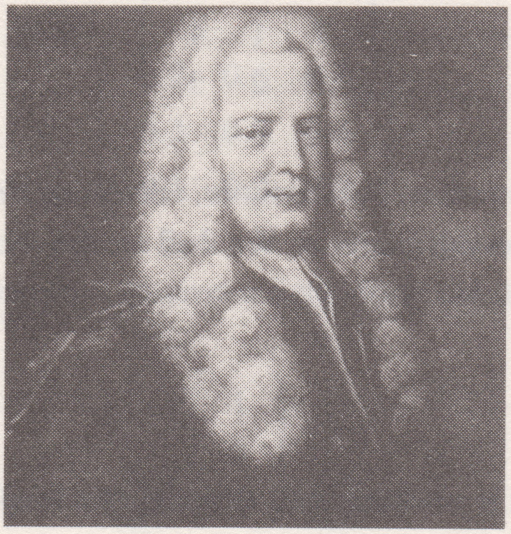
the determinant of the matrix A, will be:

$$|A| = \begin{vmatrix} a & b \\ c & d \end{vmatrix}$$

where the value of the determinant is $a \cdot d - b \cdot c$. In other words, we multiply the elements of the main diagonal and subtract the product of the secondary diagonal. For example, the determinant of the matrix A is 2, because:

$$A = \begin{pmatrix} 2 & 1 \\ 4 & 3 \end{pmatrix}, \ |A| = \begin{vmatrix} 2 & 1 \\ 4 & 3 \end{vmatrix} = (2) \cdot (3) - (4) \cdot (1) = 6 - 4 = 2.$$

It is important to note that we have changed the large brackets used to represent a matrix, replacing them with two parallel bars, the standard notation for the determinant. Curiously, determinants came before matrices and were known by the 3rd century BC



The Swiss mathematician Gabriel Cramer (1704–1752) coined the rule named after him that uses determinants to solve systems of linear equations.

in China. The ancient Chinese used something similar to a determinant, arranging the unknowns of a system of linear equations on a chessboard. However, it was not until 1750 in Europe that the mathematician Cramer was able to use determinants to solve systems of linear equations. At the dawn of the 19th century, other mathematicians, such as Cauchy, also worked with determinants. Matrices arrived later on, receiving the name matrix to highlight the 'mother' role played by determinants.

One of the properties of determinants is their order. This property refers to the number of rows and columns of the determinant. Hence, for example, an order 1 determinant will contain just one element; an order 2 determinant will have two rows and two columns; if the determinant is of order 3, it will have three rows and three columns, and so on:

$$|a_{11}|, \quad \begin{vmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{vmatrix}, \quad \begin{vmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{vmatrix}, \text{ etc.}$$

In fact, the value of a determinant of order one will be the only element it contains, or rather, a_{11}. Furthermore, we have shown above how to calculate a determinant of order 2, but how do we calculate a determinant of order 3?

The determinant of a square 3 × 3 matrix

Sarrus' rule is perhaps one of the best-known methods. However, the method described below is more useful. As mathematicians say, imagine a square matrix of order 3:

$$A = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}$$

Each position of the matrix has a sign + or −, so if we were dealing with a sodium chloride crystal (better known as common salt):

$$\begin{pmatrix} + & - & + \\ - & + & - \\ + & - & + \end{pmatrix}$$

We select, for example, the first row of the matrix and eliminate it. We now erase the first column of the matrix:

$$\begin{pmatrix} a_{11} & \cdots & \cdots \\ \vdots & a_{22} & a_{23} \\ \vdots & a_{32} & a_{33} \end{pmatrix}$$

carrying out the following operations with the elements:

$$a_{11} \cdot \begin{vmatrix} a_{22} & a_{23} \\ a_{32} & a_{33} \end{vmatrix} = a_{11} \cdot (a_{22} \cdot a_{33} - a_{23} \cdot a_{32}).$$

Note that a_{11} is positive because of the sign corresponding to its position in the matrix.

Once we have removed the first row and the first column, the remaining elements give a new matrix. The result of this matrix is referred to as a minor M_{ij}, where i and j are the numbers of the row and column that have previously been eliminated, $i = 1$ and $j = 1$ in the example.

The same thing is done with the second column:

$$\begin{pmatrix} \cdots & a_{12} & \cdots \\ a_{21} & \vdots & a_{23} \\ a_{31} & \vdots & a_{33} \end{pmatrix}$$

and since the element a_{12} is negative, we have:

$$-a_{12} \cdot \begin{vmatrix} a_{21} & a_{23} \\ a_{31} & a_{33} \end{vmatrix} = -a_{12} \cdot (a_{21} \cdot a_{33} - a_{23} \cdot a_{31}).$$

Finally, these operations are repeated for the third column:

$$\begin{pmatrix} \cdots & \cdots & a_{13} \\ a_{21} & a_{22} & \vdots \\ a_{31} & a_{32} & \vdots \end{pmatrix}$$

Since the sign for a_{13} is positive, we have:

$$a_{13} \cdot \begin{vmatrix} a_{21} & a_{22} \\ a_{31} & a_{32} \end{vmatrix} = a_{13} \cdot (a_{21} \cdot a_{32} - a_{22} \cdot a_{31}).$$

Once these operations have been carried out, the determinant of the matrix A is obtained by bringing together the previous results in a single expression:

$$a_{11}(a_{22} \cdot a_{33} - a_{23} \cdot a_{32}) - a_{12}(a_{21} \cdot a_{33} - a_{23} \cdot a_{31}) + a_{13}(a_{21} \cdot a_{32} - a_{22} \cdot a_{31}).$$

For example, given the matrix A:

$$\begin{pmatrix} 2 & 4 & 1 \\ 3 & 7 & 5 \\ 6 & 1 & 4 \end{pmatrix}$$

its determinant is calculated as follows:

$$2\begin{vmatrix} 7 & 5 \\ 1 & 4 \end{vmatrix} - 4\begin{vmatrix} 3 & 5 \\ 6 & 4 \end{vmatrix} + 1\begin{vmatrix} 3 & 7 \\ 6 & 1 \end{vmatrix} = 79.$$

Let us now imagine that three vectors coincide on the same vertex. For example,

$$\vec{u} = (2,-1,4),\ \vec{v} = (3,3,-2) \text{ y } \vec{w} = (-3,2,1).$$

Calculating the determinant

$$\begin{vmatrix} 2 & -1 & 4 \\ 3 & 3 & -2 \\ -3 & 2 & 1 \end{vmatrix}$$

gives 71. But what does this value mean? In the example above, and since the vectors coincide on the same vertex, the value of the determinant will be the volume of the parallelepiped given by the three vectors.

Dividing matrices: the inverse of a matrix and its applications in biology

A curious property of matrix operations is that it is not possible to divide one matrix by another. However, thanks to the usual ingenuity of mathematicians, there is a way of carrying out this operation. Imagine that we wish to decide 5 by 2, i.e. 5/2, with the restriction that we cannot use the procedure for division. Remember that:

$$\frac{5}{2} = 5 \cdot \frac{1}{2} \text{ and } 5 \cdot \frac{1}{2} = 5 \cdot 2^{-1}.$$

Hence, replacing the numbers 5 and 2 by the matrices A and B, we have:

$$\frac{A}{B} = A \cdot B^{-1},$$

where B^{-1} is the inverse matrix of B. Note that if we now multiply $B \cdot B^{-1}$ the result will be the identity matrix I. It is important to note that the matrix B must be square, meaning that it must have the same number of rows and columns. Furthermore, for B to have an inverse, the determinant of B must be non-zero.

There are many important applications for the inverse of the matrix. Although it is not hard to calculate the inverse of a 3 × 3 matrix, it is a little onerous, and the curious reader will find information for obtaining the inverse. However, the inverse of a 2 × 2 matrix can be obtained as follows. Imagine a matrix A:

$$\begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

Its inverse A^{-1} can be obtained directly and is equal to:

$$\begin{pmatrix} a & b \\ c & d \end{pmatrix}^{-1} = \frac{1}{ad - bc} \begin{pmatrix} d & -b \\ -c & a \end{pmatrix}$$

Remember that $1/(ad - bc)$ is the inverse of the determinant of the matrix. For example, and although the intermediate steps are not provided, using the symbolic computation programme Derive, gives the following inverse of matrix A:

$$\begin{pmatrix} 3 & 2 & 5 \\ 6 & 9 & 1 \\ 2 & 7 & 8 \end{pmatrix}$$

Typing the command A^(−1) into the programme gives A^{-1}, or rather the inverse of the matrix:

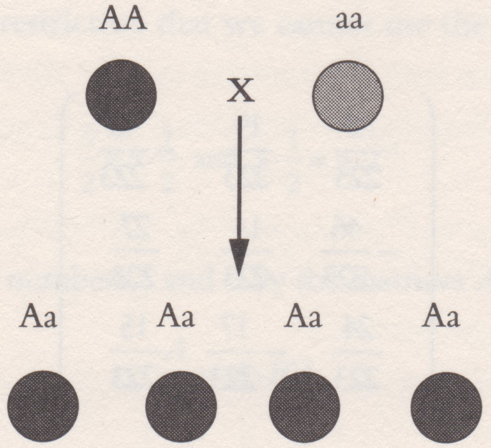
$$\begin{pmatrix} \frac{65}{223} & \frac{19}{223} & -\frac{43}{223} \\ -\frac{46}{223} & \frac{14}{223} & \frac{27}{223} \\ \frac{24}{223} & -\frac{17}{223} & \frac{15}{223} \end{pmatrix}$$

The inverse of a matrix is commonly used in three-dimensional (3D) computer simulations, whereas matrix multiplication is useful for carrying out rotations, for example with a computer simulation of a dinosaur head. Such simulations are currently the order of the day in biomedicine. It is also useful for encrypting – and hence protecting – messages. Furthermore, it is fundamental to some of the most important statistical techniques of so-called multivariate analysis, a collection of statistical methods that is highly useful in the analysis of experimental data in biology and medicine. However, perhaps the most interesting application is the method for solving systems of linear equations to be discussed in the following chapter.

Matrices and peas: Mendel's laws

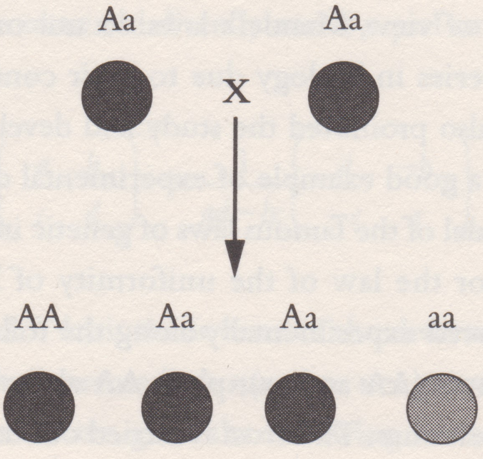
From a historical point of view, Mendel's laws do not only represent one of the ground-breaking discoveries in biology due to their contribution to the birth of genetics, but they have also promoted the study and development of mathematical biology by representing a good example of experimental design. In this section, we shall consider a basic model of the famous laws of genetic inheritance using matrices.

Mendel's first law, or the law of the uniformity of hybrids (Aa) in the first generation F_1, was deduced experimentally along the following lines. Imagine we cross two pure-bred plants (AA and aa); plant AA always gives yellow seeds and plant aa always gives green ones. The cross is carried out using the cross-pollination method: we use scissors to cut the stamens of the receptor plant, i.e. aa, hence avoiding its self-pollination. We then use a brush to collect pollen from the stamens of the donor plant, AA, fertilising the receptor plant aa by impregnating the opening of its carpel using the brush. Observing the offspring A, which Mendel called the first generation offspring, or F_1, all the peas were yellow and of the hybrid type Aa.



Mendel's first law.

After completing the experiments that led Mendel to discover his first law, the researcher decided to study another property of this generation. He asked whether the yellow peas (F_1) obtained in the experiments were all equal to the pure-bred peas (AA) of the parent generation. How did he find the answer? Mendel designed an ingenious experiment. The monk self-pollinated the peas of generation F_1 and subsequently noted the offspring of a total of 8,023 peas. After meticulously counting the number of yellow and green peas, he found that 3/4 of the plants were yellow and the remaining 1/4 green. This result shaped the second of his laws, the law of segregation of characteristics in the second generation.



Mendel's second law.

Formulating the second law using matrices gives:

$$\begin{pmatrix} \frac{3}{4} \\ \frac{1}{4} \end{pmatrix}$$

Note that this vector captures the properties referred to by geneticists as phenotypic segregation. Furthermore, adding their elements together, in this case those of the single column, gives 1. In mathematical biology, this is known as a stochastic vector. Square matrices with this property are referred to as stochastic matrices.

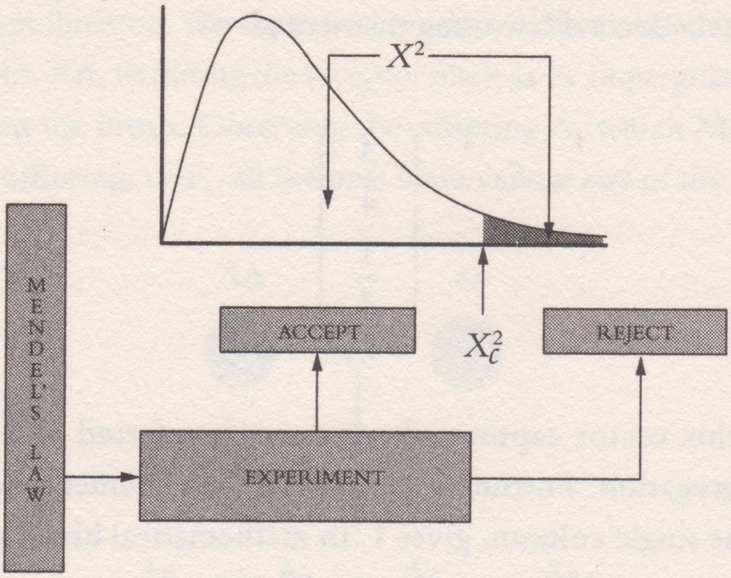
Imagine we carry out an experiment in a 'Mendelian' allotment, yielding 660 peas. We then count the number of yellow peas and the number of green peas. If we find that 510 are yellow and 150 are green, do our results conform to Mendel's second law? In order to check this, we must ask how many yellow and green peas should have been obtained according to this law. Multiplying the total number of peas of the descendants, 660, by the column vector that conforms to the second law:

$$660 \cdot \begin{pmatrix} \frac{3}{4} \\ \frac{1}{4} \end{pmatrix}$$

gives the vector:

$$\begin{pmatrix} 495 \\ 165 \end{pmatrix}$$

Or rather, according to Mendel's second law, we should have obtained 495 yellow peas and 165 green ones. What conclusions can we draw? We shall now describe the procedure used by geneticists to check if the data of an experiment conforms to a mathematical law. Let's check if our results conform to Mendel's second law.



A diagram of the experimental method applied to Mendel's inheritance laws, a fundamental part of mathematical biology.

To do so, we shall make use of one of the most popular statistical tests in biology, known as the chi-squared test. Without going into too much detail regarding this statistical test, we calculate the sum of the following expressions, which we use to assess the deviation of our results with respect to the values we should have obtained according to Mendel's second law. We represent this number using the Greek letter χ (chi):

$$\chi^2 = \frac{(510-495)^2}{495} + \frac{(150-165)^2}{165} = 0.45 + 1.36 = 1.81.$$

We then compare the sum with a reference value, referred to as the chi-squared critical value and represented as χ_c^2. For elementary Mendelian experiments, the value of χ_c^2 is 3.84. Finally, we apply the following criterion. If the sum of χ^2 is greater than the value $\chi_{c,}^2$ we conclude that our results do not conform to the predictions of Mendel's second law. Otherwise, if the sum χ^2 is less than the value χ_c^2, the experimental results do conform to the predictions of the second law. Since 1.81 is less than the critical value of 3.84, we can conclude that the results of the experiment conform to this law.

Hence, the differences between our data, 510 and 150, and those predicted by the theory, 495 and 165, are due to the effects of chance and do not have experimental significance.

Is inheritance independent?

Remember that Mendel's second law states that the different choices for a gene, A or a, are transmitted independently. The researcher then dared to take a step further, asking if the two properties appeared simultaneously in an individual specimen, how are they transmitted to the following generation? Is their inheritance independent? In order to find the answer, Mendel designed the following experiment.

Let's say that the following properties can be easily observed in peas: their appearance can be smooth (A) or rough (a); and their colour can be yellow (B) or green (b). Once Mendel had decided on these two properties, he crossed two pure breeds, one of smooth, yellow peas (AABB) and another of rough, green peas (aabb). The plants of these crossbreeds represented the parental generation P, with which he obtained the corresponding descendants for the first generation offspring F_1. Note how the gametes produced by the AABB plants were all of type AB, whereas all the gametes produced by the aabb plants were type ab. Hence, and after cross-pollinating plants of different breeds, all the plants of F_1 produced smooth, yellow peas, with genotype AaBb.

Having reached this point of the experiment, Mendel asked himself what type of offspring could be expected from the reproduction of the AaBb plants obtained in F_1. What would the second generation offspring (i.e. F_2) look like? Mendel used the results he obtained to formulate his third law, the law of independent assortment.

AaBb × AaBb

↓

	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

Mendel's third law.

In fact, the 16 results for F_2 are obtained by combining the four classes of gametes produced by the AaBb plants in a square, or rather, AB, aB, Ab and ab. The square is referred to as a Punnett square, and is of great use when it comes to determining the offspring of F_2 in Mendel's third Law.

Note that the 16 types that have been obtained can be regrouped as follows:

- 9 smooth, yellow peas (AxBy).
- 3 rough, yellow peas (aaBy).
- 3 smooth, green peas (Axbb).
- 1 rough, green pea (aabb).

Here x can be A or a, and y B or b. Once again, formulating this law of inheritance as a matrix gives:

$$\begin{pmatrix} \frac{9}{16} \\ \frac{3}{16} \\ \frac{3}{16} \\ \frac{1}{16} \end{pmatrix}$$

Let us conclude this section by assuming that we carry out a new experiment in a Mendelian plot and obtain 1,425 peas. Counting the number of peas of each type, we obtain 807 smooth yellow peas (AxBy), 270 rough yellow peas (aaBy), 265 smooth green peas (Axbb) and 93 rough green peas (aabb). How do we check that our results agree with Mendel's third law? First of all, it is necessary to calculate the values that we should have obtained according to the third law:

$$1.425 \cdot \begin{pmatrix} \frac{9}{16} \\ \frac{3}{16} \\ \frac{3}{16} \\ \frac{1}{16} \end{pmatrix} = \begin{pmatrix} 802 \\ 267 \\ 267 \\ 89 \end{pmatrix}$$

MENDEL AND THE LAWS OF INHERITANCE

Gregor Mendel was a botanist who was born in Austria in 1822 and became an Augustinian priest in 1843, before retiring to Königskloster, in what is now the Czech Republic. In 1857, in a small allotment that was just 35 metres long and 7 metres wide, Mendel began his hybridisation experiments using peas. They would later lead to the establishment of his famous laws of inheritance.

Mendel's brilliance lay in the study of a few properties and considering them separately for the pea plant *Pisum sativum*. Crucially, Mendel distinguished between the dominant properties, represented in upper case (A, B, C…), and recessive ones, represented in lower case (a, b, c…). The best-known properties chosen by this brilliant researcher were the shape of the seed (smooth A, rough a), its colour (yellow B, green b), its appearance (smooth C, rough c), in addition to other elements that were also inherited in line with his laws, such as the position of the flower, the shape of the sheath, the colour of the sheath, etc. One of the reasons for his success was the use of pure breeds (AA, aa) and avoiding accidental self-pollination of plants during his experiments.

His main conclusion was that the inheritance of the properties can be expressed using simple mathematical laws, and he sent his results to Nägeli, a famous Swiss scientist who paid no attention to his discoveries. Mendel published his work under the title *Versuche über Pflanzenhybriden* (Experiments on Plant Hybridisation), presented in 1865 at the Brno Natural Science Society, where his work once again passed unnoticed. It appears he also wrote a letter to Darwin, telling him about the results of his experiments, although Darwin never read it. Ignored for 35 years, Mendel died in 1884 and his work would only be rediscovered at the turn of the century.

We then calculate the deviations between the results predicted by the law and those obtained experimentally to check whether they are sufficient to conform to Mendel's third law. To do so, we apply the chi-square test once again. We leave it to the reader to carry out the calculations. What is the conclusion?

Markov matrices, DNA and bioinformatics

One of the most promising areas of bioinformatics is the study of the genome of a species – the totality of the genetic information stored in the DNA of its cells. The analysis of the genomes of various species is one of the most common methods used by biologists to study the evolution of a species. To do so, a matrix is used whose elements are probabilities. Although we shall not go into details, it suffices to say that the probability is a measurement of the frequency with which a result occurs in a phenomenon or random experiment. The measurement is a number between 0 and 1. When the result of an experiment is impossible, we say its probability is zero; if one result always occurs, its probability is 1. For example, if we throw a die, the probability of obtaining a result {1, 2, 3, 4, 5, 6} is 1/6, whereas the probability of the result being even {2, 4, 6} is 1/2.

One property of these experiments in which a die is thrown or a coin tossed is the absence of memory. In other words the result obtained is independent of the results previously obtained in a similar experiment. However, the mathematician Andrei Markov studied phenomena with memory, known as the Markov chain. In a Markov chain, the probability of getting a result depends on the previously obtained result. They are experiments or phenomena that 'remember' the last result, which affects the possibilities for future results. For example, when it comes to DNA, the probability that at a future time $t + 1$ a certain point in the chain has a base {A, T, G, C} (adenine, thymine, guanine and cytosine) depends on the base of the position in the chain at the previous time t.

Taking into account all the possible changes or mutations that a given DNA unit, or base, can suffer, we get the following matrix:

$$\begin{pmatrix} P_{AA} & P_{AT} & P_{AG} & P_{AC} \\ P_{TA} & P_{TT} & P_{TG} & P_{TC} \\ P_{GA} & P_{GT} & P_{GG} & P_{GC} \\ P_{CA} & P_{CT} & P_{CG} & P_{CC} \end{pmatrix}$$

For example, and according to this matrix, for a given DNA molecule the probability that an adenine (A) subunit changes to cytosine (C) at a given point in the chain has a probability of p_{AC}.

Markov chains are used to predict protein coding regions in the genome, as well as for studies on speciation – the evolution of species. This type of model is also used for studies on the structure of proteins.

Chapter 5

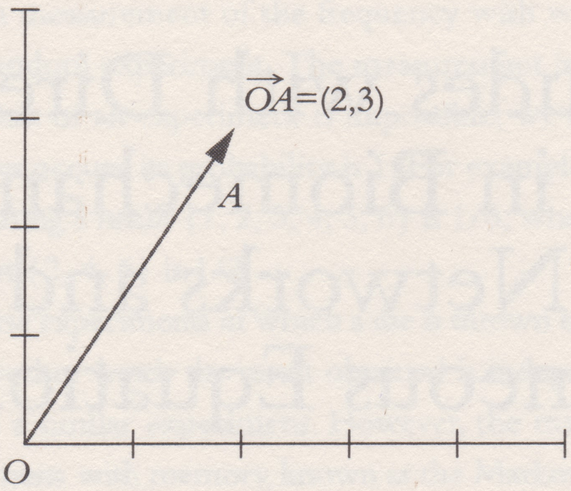
Magnitudes with Direction: Vectors in Biomechanics, Neural Networks and Simultaneous Equations

In everyday life we are used to measuring certain things, such as the temperature of a room or the weight of a bag of sweets. In the laboratory, a chemist often measures the acidity of a substance by calculating its pH, and a biologist measures the partial pressure of O_2 (oxygen) using a bioreactor. All these measurements have a common property – their value does not depend on the direction and sign of the measurement. For example, generally speaking the ambient temperature will not depend on the location of the thermometer. In the case of the pH, it is assumed that the substance is sufficiently homogeneous – the measurement will not be affected by the position of the indicator. Since they reduce values to a single number, these types of measurements are called scalar magnitudes.

However, there are many other situations in which the direction or sign are just as important as the value measured. For example, in physics, speed, acceleration, force, the electrical field and gravity do not only have a specific number, but also a direction and sign. When it comes to vertebrate biology, the contraction mechanism for musculature is such that a muscle can only pull in one direction. Where the magnitude and direction are measured together we produce a vector magnitude.

Vectors and matrices

As their name suggests, vector magnitudes are represented using a mathematical object referred to as a vector. This has a numerical value called its modulus, which corresponds to its length and is the value represented by the magnitude, such as the speed. However, it also has a direction, and as part of this direction, a sign.



Vector on a plane xy.

However, what is the relationship between vectors and matrices? Matrix operations constitute an easy way of carrying out operations on vector magnitudes, which, as we can easily see, do not only have applications in science and technology, but also in numerous aspects of everyday life.

Hence, a matrix with a given number of rows, *m*, and a single column constitutes, in matrix notation, a vector. Hence, the matrix is an $m \times 1$ column vector. Vectors are represented using the notation $\vec{u}$, $\vec{v}$,etc. For example, the vector $\vec{u}$:

$$\begin{pmatrix} u_1 \\ u_2 \\ \vdots \\ u_m \end{pmatrix}$$

It also seems logical to think that the number of elements of the vector *m* is related to some important property. This is indeed the case, since this number corresponds to the dimensions of the space in which we are working. Specifically, the vector:

$$\begin{pmatrix} 2 \\ 7 \end{pmatrix}$$

represents a vector magnitude on a plane; the vector's origin is (0,0) and its end is (2,7). The following vector does so in space (obviously three dimensional):

$$\begin{pmatrix} 3 \\ 1 \\ 5 \end{pmatrix}$$

where its origin is the point (0,0,0), and the end corresponds to the point with coordinates (3,1,5).

However, what is the magnitude represented by a vector? The method used for obtaining this value, also referred to as the modulus, is simple. Given the vector $\vec{u}$, it is enough to calculate:

$$\sqrt{u_1^2 + u_2^2 + \ldots + u_m^2}\,.$$

In mathematical notation, the modulus is represented between two bars, for example $|u|$. For the two vectors above, their value or modulus is:

$$\sqrt{2^2 + 7^2} = 7.28 \text{ and } \sqrt{3^2 + 1^2 + 5^2} = 5.91.$$

VECTOR SPACE

The study of matrices and simultaneous linear equations led to the concept of vector space in the 17th century. Although we shall avoid entering into the details, from a mathematical point of view the possibility of adding vectors (i.e. $\vec{u}+\vec{v}$) and multiplying a given number k by a factor $\vec{u}$ (i.e. $k \cdot \vec{u}$) allows us (together with certain properties) to define a specific set of vectors as a vector space. This is an essential concept in mathematical biology and has been used for applications such as phylogenetic studies, the classification of DNA sequences, ecological models (such as population growth), research into metabolic paths and the perception of colours.

By definition, mathematicians understand that, unless otherwise specified, the term vector refers to a column vector.

The transposition symbol can be used to define row vectors:

$$(u_1\ u_2\ \dots\ u_m).$$

The concept of a vector space is one of the most important in mathematical biology with the greatest number of applications in this field.

We will now consider these ideas with respect to animal locomotion and neural networks.

Vector addition: muscular contraction and animal locomotion

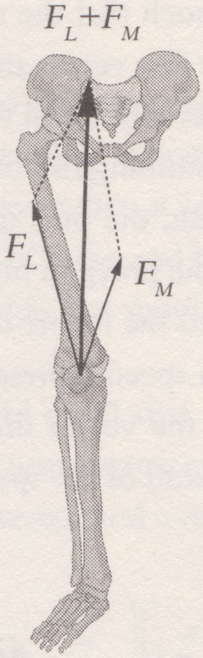
One of the most interesting applications of vectors is in the study of animal locomotion. Grasshoppers jump, humans can lift a weight voluntarily using their arms, fish dive and swim and birds glide and fly. The introduction of vectors makes it possible to understand the mechanical nature of these examples of animal kinetics.

It is possible to associate a vector with an arm's biceps muscle, which represents the force resulting from a muscular contraction in the upper arm, a second vector to represent the reaction force at the turning point of the elbow, and finally, a third vector to represent the weight of an object held in the hand.

It is possible to understand the function of certain muscles in the human body using the sum of the vectors. One of the methods for adding two vectors is the well-known parallelogram rule. The procedure consists of joining the two vectors that we want to sum in order to calculate their origin. We then draw a parallelogram, until the two lines parallel to the vectors meet.

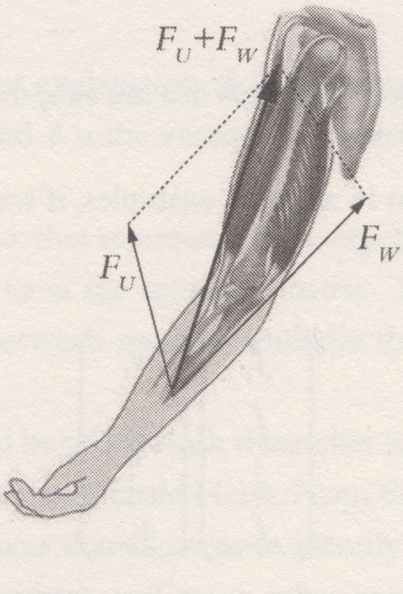
For example, if we consider a leg and represent the side portion of the quadriceps by the vector $\vec{F}_L$ and the middle portion of the muscle by the vector $\vec{F}_M$, it is possible to obtain the sum of both forces, or rather the two vectors $\vec{F}_L + \vec{F}_M$ using the rule above. It gives the total force of the quadriceps muscle represented by the sum of vectors $\vec{F}$.

The following diagrams provide a clearer explanation of how these forces act in particular parts of the body.



Sum of the vectors of the leg using the parallelogram rule.

Another classic example is the force $\vec{F}$ exerted by the flexor muscle of the forearm. Represented as a vector, the force of this muscle is the result of the sum of another two vectors with an anatomic representation. One of the factors, which we shall call $\vec{F}_U$, is perpendicular to the forearm and the other vector, $\vec{F}_W$, is parallel.

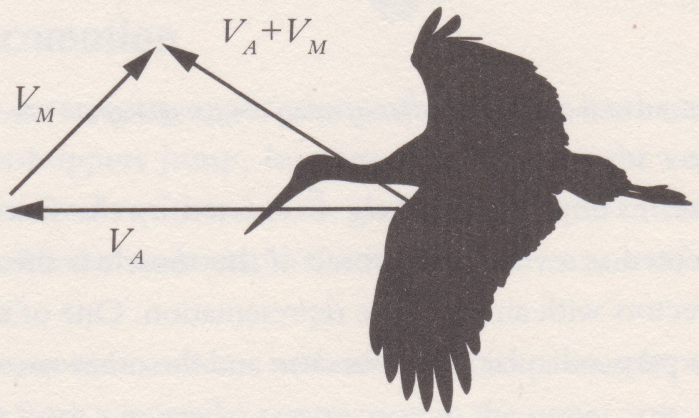


Sum of the vectors of the arm using the parallelogram rule.

However, it is also possible to add more than two vectors, in which case we can use the polygon of forces method. This method involves joining the end of one vector to the origin of the next, such that the sum or total vector is such that its origin is joined to the origin of the first vector and its end coincides with the end of the last vector. This method is especially useful when it comes to calculating sailing speed or the displacement of a swimming fish or the flight of birds.

In the cases of the birds and fish, the final speed of the animals' motion is the sum of just two vectors. Even so the polygon method is used in these cases instead of the parallelogram method due to the nature of the problem.

Imagine that a bird moves at a speed represented by the vector $\vec{V}_A$, where $\vec{V}_M$ is the speed of the wind. Hence, the vector that expresses the resulting speed $\vec{V}$ at which the animal moves is the sum of the speeds $\vec{V}_A$ and $\vec{V}_M$, obtained using the polygon technique.



The sum of the vectors of the flight of a bird using the polygon technique.

We must remember that in all these examples, if we wish to obtain the result as a column vector, such as $\vec{F}$, $\vec{V}$:

$$\begin{pmatrix} f_1 \\ f_2 \\ \vdots \\ f_m \end{pmatrix}, \begin{pmatrix} v_1 \\ v_2 \\ \vdots \\ v_m \end{pmatrix}$$

it is necessary to add in the same way as for matrices, that is to say $\vec{F}_U+\vec{F}_W$, $\vec{F}_L+\vec{F}_M$ and $\vec{V}_A+\vec{V}_M$ respectively.

Vector multiplication and its application to neural networks

As well as adding two vectors and applying them to the study of animal movements and biomechanics, there are other operations using vectors with numerous applications in the most diverse areas when it comes to studying life. The product or multiplication of vectors is one of these, and has been successfully applied to the development of mathematical models that simulate some of the most characteristic tasks of the brain.

Hence, for example, we should recall that when it comes to describing the operations that can be carried out using matrices, we made use of a neural network model based on the product of a vector and a matrix:

$$\begin{pmatrix} c_{11} & c_{12} & \cdots & c_{1j} \\ c_{21} & c_{22} & \cdots & c_{2j} \\ \vdots & \vdots & \cdots & \vdots \\ c_{m1} & c_{m2} & \cdots & c_{mj} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_m \end{pmatrix} = \begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{pmatrix}$$

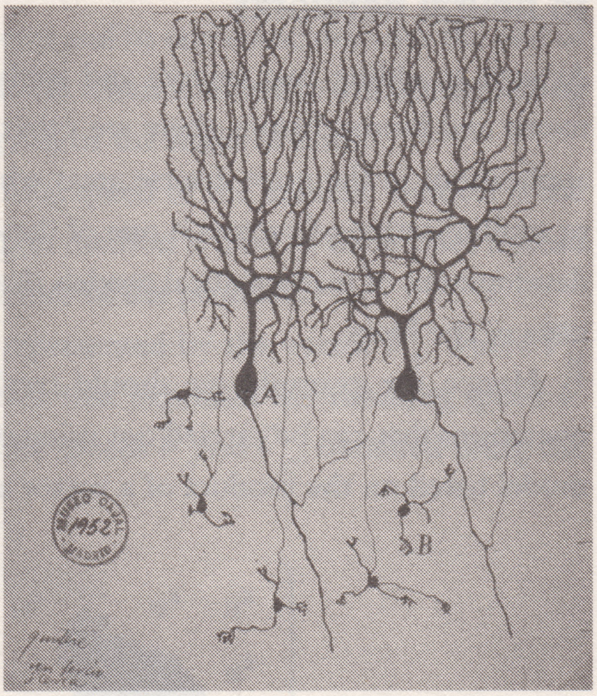
The neural network can also be expressed in a simpler way as:

$$M \cdot \vec{u} = \vec{v}.$$

In line with our previous explanation, $\vec{u}$ is the vector that represents the input layer or afferent neurons, and $\vec{v}$ is the vector that represents the output or efferent neurons.

Similarly, M is the matrix that represents the connections between the neurons of the two layers, referred to as the memory matrix. This name is related to the fact that the connections between neurons underlie the way the brain stores our memories.

This idea was introduced by the Spanish researcher Santiago Ramón y Cajal and later developed by the American Donald Hebb. From then on, neuroscientists have believed that the facial features that allow us to identify our friends (and enemies), the shapes of letters and numbers, and many other patterns are stored using these connections.



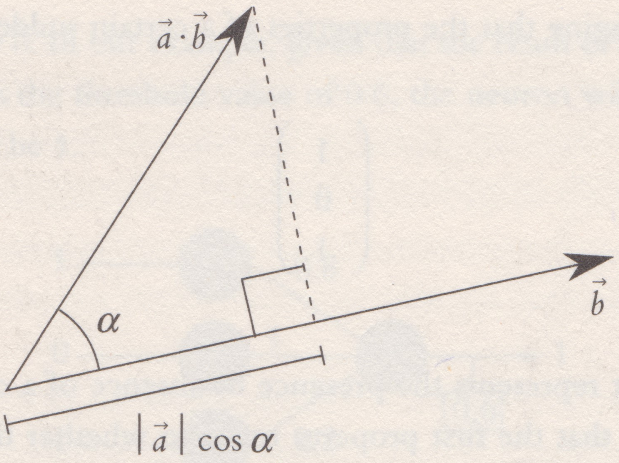
Left, Santiago Ramón y Cajal (1852–1934) in the lab; right, one of his drawings of neural networks.

Consequently, if we take an arbitrary row of the matrix *M* as a row vector containing the connections between a certain output neuron and all those of the input layer, the calculation of the state of this output neuron is obtained as described in the previous chapter. The operation between such vectors is known as the scalar product of two vectors. For example, imagine two vectors, a row vector $\vec{a}$ (to which we add the sign *t* to denote the transpose in mathematical notation) and a column vector $\vec{b}$. The scalar product of the two vectors is equal to:

$$\vec{a}^t \cdot \vec{b} = \begin{pmatrix} 1 & -3 & 5 \end{pmatrix} \begin{pmatrix} 2 \\ 6 \\ 4 \end{pmatrix} = (1)\cdot(2) + (-3)\cdot(6) + (5)\cdot(4).$$

Carrying out the appropriate arithmetic operations, gives the end result of 4.

The scalar product is also called the inner product of two vectors, giving a number whose meaning is the value of the projection of the row vector $\vec{a}$ onto the vector $\vec{b}$. If we know the length of two vectors, written as $|\vec{a}|$ and $|\vec{b}|$, in addition to the angle α between them, the scalar product $\vec{a} \cdot \vec{b}$ will be equal to $|\vec{a}| \cdot |\vec{b}| \cdot \cos \alpha$. This result is of particular interest for our purposes if we bear in mind that $|\vec{a}| \cdot \cos \alpha$ is the value of the projection of the vector $\vec{a}$ on the vector $\vec{b}$.



The scalar or inner product of two vectors $\vec{a}\cdot\vec{b}$.

PUSHING OBJECTS: WHAT IS WORK?

The work we do when we push an object across the floor is another example that illustrates the usefulness of the scalar product. According to classical mechanics, work is defined as the scalar product of the force $\vec{F}$ exerted on the object and the resulting displacement $\vec{D}$. Hence, if the vectors $\vec{F}$ and $\vec{D}$ form an angle α, the work W will be equal to $|F|\cdot|D|\cdot\cos\alpha$. Note that using the same force $\vec{F}$ it is possible to obtain more or less work depending on the angle between the vectors. Essentially, work is greatest when both vectors, $\vec{F}$ and $\vec{D}$, have the same direction, or in other words the angle α is equal to 0, since the cosine of 0 is 1. Similarly, it is clear that for values of the angle α above 0°, the work will be below this maximum value.

Learning: the case of capturing sound

Since the beginning of the 20th century, thanks to the work of Santiago Ramón y Cajal, neuroscientists have known that the biological mechanism for learning consists of the modification of the connections between neurons, referred to as synapses. From the perspective of mathematical biology, animal or human learning can be simulated by simply changing one or more of the values of the connections represented by the row vector $\vec{a}$.

The result is that after this change, or rather after the learning, the value or state of the output or efferent neutron will change, and hence the subject's response to a certain stimulus.

For example, imagine that the properties of a certain sudden sound are given by the vector:

$$\begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix}$$

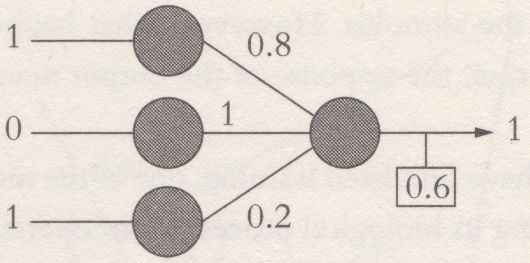
where each element represents the presence or absence of a certain property of the sound. Imagine that the first property refers to whether the intensity of the sound is more than 30 decibels (1) or less than this value (0). A value of 30 decibels represents, for example, a street without traffic, and the sound made when turning the pages of a book is quieter. The second property refers to the frequency and is (1) if this is within the range 100–5,000 Hertz, which represents the majority of sounds or noises that cause annoyance, and is (0) if it falls outside this range. Finally, the third property contained in this vector is the power of the sound, which is (1) if the value is greater than 1 Watt, which corresponds to the sound produced by a pneumatic drill or the engine of an aircraft. Otherwise, it is (0) for values below 1 Watt, for example the sound produced by a car, a piano, a conversation, etc.

Let us now imagine that the connections between the three neurons of the input or afferent layer (the function of which is to 'greet' this vector using the information about the sound that is received by the ears) are connected to a neuron on the output or efferent layer, where the connections are as follows:

$$\begin{pmatrix} 0.8 & 1 & 0.2 \end{pmatrix}.$$

Taking the scalar product of the two vectors, the state of the output neuron is equal to 1.0, since it is $(0.8) \cdot (1) + (1) \cdot (0) + (1) \cdot (0.2)$.

Let us now imagine that an improvement is made to the neuron on the output layer to make the model more realistic. Hence if the neuron is stimulated, it responds if the output value exceeds the value of a certain arbitrarily defined threshold. For example, let θ be that threshold value, which is set at 0.6. This means that if the result of the scalar product is greater than or equal to θ, the neuron will be stimulated. Let us call this state 1. Otherwise, if the scalar product is less than θ, the neuron will not have received sufficient stimulus, and will remain at rest in the state represented by 0. In our example, given that the result of the scalar product is one, which exceeds the threshold value of 0.6, the neuron will be stimulated and hence its status will be 1.

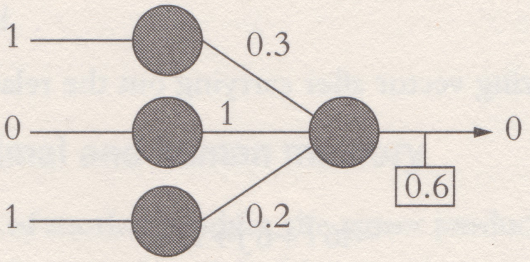


An example of the neural network prior to training.

But what happens if the person is exposed to various sounds? What happens when he or she learns? In this case, it changes the value of the connections. Imagine, for example, that after a training session, the value of the subject's questions has changed. Specifically:

$$\begin{pmatrix} 0.3 & 1 & 0.2 \end{pmatrix}.$$

This means that the importance of this connection has reduced from 0.8 to 0.3, giving less importance to the decibels of the sound signal. Taking the scalar product, or rather if the neural network is simulated using the same stimulus, after the learning, the state of the output neuron is 0.5, since it can be seen that it is equal to (0.3) · (1) + (1) · (0) + (1) · (0.2). If we now compare the state of the efferent neuron with the threshold value θ, 0.6, the neuron now remains in a state of rest, in state 0.



An example of the neural network after training.

Note that the learning can be interpreted as the rotation of the row vector of connections $\vec{a}$ on $\vec{b}$. The larger the projection of the vector of connections $\vec{a}$ onto the vector with the stimulus $\vec{b}$, the larger the response of the output neuron.

Hence, the response of the neuron is greatest when the connection vector has the same direction as the stimulus. However, what happens if both vectors are perpendicular? In this case, the response of the output neuron will be 0, since cos 90 is 0.

To summarise, we have simulated learning, one of the most fascinating functions of the brain, interpreting its biological process by an operation using vectors. This mathematical model was introduced by McCulloch and Pitts in 1946, and from then on has formed the basis of a considerable number of models used to simulate different aspects of the brain using basic neural networks.

The vector or outer product

Another way of multiplying or taking the product of two vectors is the vector product, also referred to as the outer product of two vectors.

Let us use the same vectors from the example for the scalar product to explain this procedure. Imagine two vectors, a vector $\vec{a}$ and another $\vec{b}$. The vector product of two vectors is equal to:

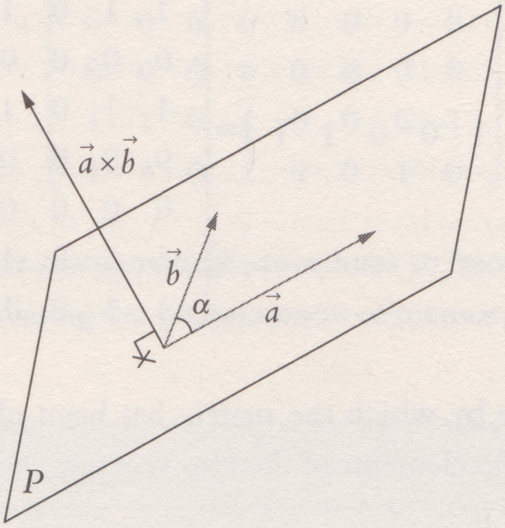
$$\vec{a} \times \vec{b} = \begin{vmatrix} \hat{i} & \hat{j} & \hat{k} \\ 1 & -3 & 5 \\ 2 & 6 & 4 \end{vmatrix} =$$

$$= \begin{vmatrix} -3 & 5 \\ 6 & 4 \end{vmatrix} \hat{i} - \begin{vmatrix} 1 & 5 \\ 2 & 4 \end{vmatrix} \hat{j} + \begin{vmatrix} 1 & -3 \\ 2 & 6 \end{vmatrix} \hat{k}$$

which gives the following vector after carrying out the relative arithmetic operations:

$$-46\,\hat{i} + 6\,\hat{j} + 12\hat{k}.$$

Note that we can distinguish this type of product from the scalar product by using the operator ×. Furthermore, while the result of the scalar product is a number, for the vector product the result is a vector. Another difference that should be noted is that while the scalar product $\vec{a}^t \cdot \vec{b}$ represents the projection of the row vector $\vec{a}$ onto a column vector $\vec{b}$, the result of the vector product $\vec{a} \times \vec{b}^t$ is a vector, which we write as $\vec{c}$, perpendicular to the plane defined by the two vectors.



The vector or outer product of two vectors $\vec{a} \times \vec{b}$.

In fact, the value or modulus of this new vector $\vec{c}$, the result of the operation, recalls the scalar product, except that now it is equal to $|\vec{a}| \cdot |\vec{b}| \cdot \sin \alpha$, the final numerical value of which is precisely the area of the parallelogram constructed by the two vectors. The direction of the vector $\vec{c}$ is obtained using the so-called 'right-hand rule'.

In biology, the study of the molecules that are essential to life uses the vector product. This is the case for proteins, such as myoglobin, and the most famous molecule of all those described so far, the DNA molecule. These biophysical studies use classical concepts from physics, measuring magnitudes whose calculation is based precisely on what we have called the vector $\vec{c}$. One example is the dipole moment, the calculation of the magnetic force to which a particle is subjected inside a magnetic field.

A model of the animal and human memory

There is an application of another product, the tensor product, that is of considerable interest, whereby a mathematical model of the neural network for animal or human memory is constructed and simulated on a computer. For example, imagine a vector $\vec{v}$ made up of just ones and zeros, in other words, a binary vector. Each of the elements of the vector represents the presence (1) or absence (0) of a certain property of a given object. Taking the tensor product of $\vec{v}$ and $\vec{v}$ gives the following matrix:

$$\begin{pmatrix} 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 1 \end{pmatrix} \begin{pmatrix} 1 & 1 & 0 & 1 & 0 & 0 & 1 & 1 \end{pmatrix} = \begin{pmatrix} 1 & 1 & 0 & 1 & 0 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 & 0 & 0 & 1 & 1 \end{pmatrix}$$

Note the procedure by which the matrix has been obtained is based on the following products of the elements of the two vectors:

$$\begin{pmatrix} (1)\cdot(1) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(1) \\ (1)\cdot(1) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(1) \\ (0)\cdot(1) & (0)\cdot(1) & (0)\cdot(0) & (0)\cdot(1) & (0)\cdot(0) & (0)\cdot(0) & (0)\cdot(1) & (0)\cdot(1) \\ (1)\cdot(1) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(1) \\ (0)\cdot(1) & (0)\cdot(1) & (0)\cdot(0) & (0)\cdot(1) & (0)\cdot(0) & (0)\cdot(0) & (0)\cdot(0) & (0)\cdot(1) \\ (0)\cdot(1) & (0)\cdot(1) & (0)\cdot(0) & (0)\cdot(1) & (0)\cdot(0) & (0)\cdot(0) & (0)\cdot(0) & (0)\cdot(1) \\ (1)\cdot(1) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(1) \\ (1)\cdot(1) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(0) & (1)\cdot(0) & (1)\cdot(1) & (1)\cdot(1) \end{pmatrix}$$

In spite of its apparent difficulty, which is only 'visual', the procedure is in fact simple. The matrix that is obtained is a memory matrix with the property that it 'memorises' the object 'shown' to the neural network. The idea is to use a computer to simulate the ability of people and animals to memorise other beings and objects. Given that the elements of the matrix represent connections between neurons, the model assumes that in neural networks, a neuron cannot be connected to itself. Neurons can only be connected to other neurons in the neural network. Hence, all the elements of the main diagonal must be equal to 0, and we must correct those with a value of one:

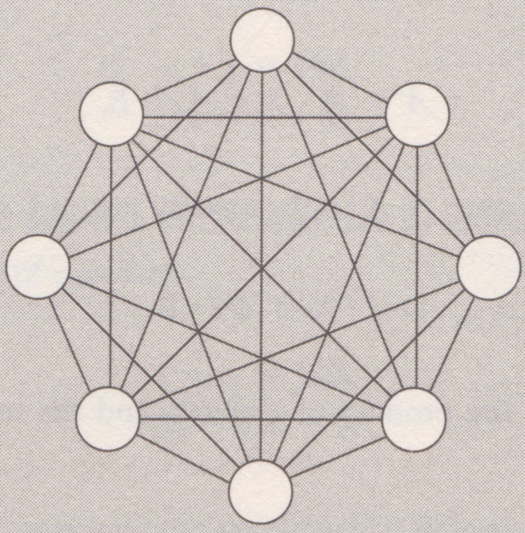
$$\begin{pmatrix} 0 & 1 & 0 & 1 & 0 & 0 & 1 & 1 \\ 1 & 0 & 0 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 & 0 & 1 \\ 1 & 1 & 0 & 1 & 0 & 0 & 1 & 0 \end{pmatrix}$$

Of course, there are mathematical procedures to 'recover' the object stored in the matrix, hence simulating the phenomenon of memory and pattern recognition.

THE HOPFIELD NETWORK

The way in which people learn, memorising letters, numbers or traffic signs, can be simulated using a neural network like those defined in this chapter. This model of memory, based on the application of the tensor product, is known as the Hopfield network, named after John Joseph Hopfield, the researcher who devised it in the 1980s.

At present, there are digital systems that use the same principle for many applications. In fact, the tensor product not only underlies many natural situations studied in physics, but is also used in digital electronics and image processing.



Hopfield memory model with eight neurons. A neuron is connected to all the cells except itself.

Solving systems of equations: what about insects?

One of the applications of the inverse of a matrix is in solving systems of equations. The idea is simple yet ingenious. Imagine a system of three equations with three unknowns, as shown below:

$$\begin{aligned} a_{11}x + a_{12}y + a_{13}z &= b_1, \\ a_{21}x + a_{22}y + a_{23}z &= b_2, \\ a_{31}x + a_{32}y + a_{33}z &= b_3. \end{aligned}$$

One of the applications of matrices allows us to use matrix notation to represent the system of equations:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix} = \begin{pmatrix} b_1 \\ b_2 \\ b_3 \end{pmatrix}$$

which can be represented by the equality:

$$A \cdot X = B.$$

Obtaining the inverse of A, i.e. A^{-1}, and multiplying both sides of the equality by the inverse matrix:

$$A^{-1} \cdot A \cdot X = A^{-1} \cdot B,$$

it can easily be seen that since $A \cdot A^{-1}$ is the identity matrix I, we have:

$$I \cdot X = A^{-1} \cdot B.$$

Furthermore, since the product of a matrix and the matrix I gives the same matrix, we have:

$$X = A^{-1} \cdot B.$$

To summarise, it is possible to solve the system, or find the values of x, y, z by taking the inverse of the matrix of the coefficients and multiplying the vector of the independent terms by this matrix.

Let us illustrate this method using an example we shall call the 'entomology experiment'. Imagine that we go out into the field to look for a specific type of insect, and set various traps in the area where we know the species is present in large numbers. After a few days, we return to collect the insects that have been captured. Upon our return to the laboratory, we count a total of 180 individuals. The individuals are classified into two groups, young individuals and adults. Let us use x to refer to the number of young individuals and y to refer to the adults. The above gives a first equation as follows:

$$x + y = 180.$$

From the data obtained some years ago as part of a similar exercise, we know that for this species of insect, the relationship between young and adult individuals that have been captured is 2 to 1, and furthermore that 6 adults have died as a result of natural causes:

$$2x = y - 6.$$

In order to determine the numbers of young and adult individuals, it is necessary to solve the following system of equations:

$$\begin{aligned} x + y &= 180, \\ 2x &= y - 6. \end{aligned}$$

Note that the second equation can be rewritten by ordering the terms as $2x - y = -6$, giving the system of equations:

$$\begin{aligned} x + y &= 180, \\ 2x - y &= -6. \end{aligned}$$

The system in our experiment can be written as follows in matrix notation:

$$\begin{pmatrix} 1 & 1 \\ 2 & -1 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 180 \\ -6 \end{pmatrix}$$

Is there a solution to a system of equations?

Mathematicians, with their usual perspicacity, have the perfectly understandable custom of not wasting time on pointless operations. One of the examples that best illustrates this is the study of types of systems. Systems of equations can be classified in terms of the number of solutions. Let us analyse the situations that may arise.

First of all, it may be the case that there is no solution to the system, in which case it is referred to as incompatible. For example, in the case of a system with two equations, specifically two straight lines, if the equations correspond to two parallel lines and do not meet at any point, it is impossible for a solution to exist. Another possibility is that the system can be solved, but there are an infinite number of solutions. In other words, if it were a system with two equations that represent two straight lines, the lines would be superimposed on each other and hence would have all their points in common.

However, what happens if the system of equations is such that the lines represented by the equations only meet at one point? In this case it is said that the system is consistent and independent, since the two lines meet at a single point (x, y), which represents the solution to the system.

A simple way of telling if a system is consistent and independent is by applying the following procedure. Imagine a system of three equations represented in matrix notation as follows:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix} = \begin{pmatrix} b_1 \\ b_2 \\ b_3 \end{pmatrix}$$

The system is consistent and independent if the determinant of the matrix A, or rather:

$$\begin{vmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{vmatrix}$$

is non-zero. Otherwise, if the determinant of A is equal to 0, the system will be consistent and dependent, or inconsistent. For example, in the entomology experiment, the system of equations can be expressed as follows in matrix notation:

$$\begin{pmatrix} 1 & 1 \\ 2 & -1 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 180 \\ -6 \end{pmatrix}$$

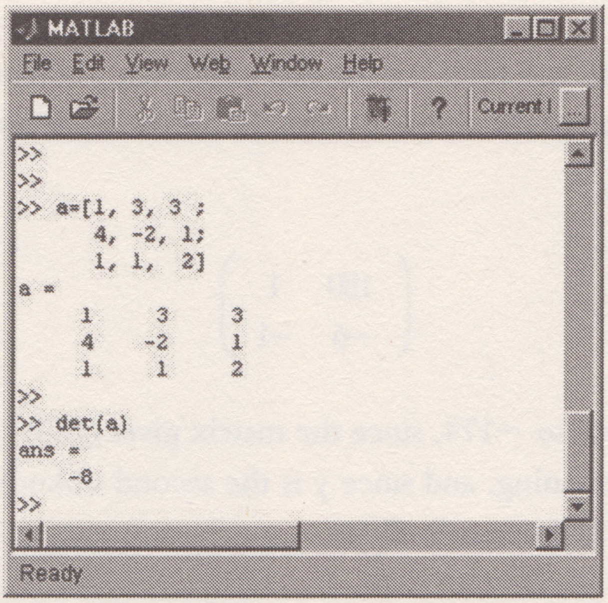
Following the criteria described, the system can be satisfactorily resolved because it is consistent and independent, since calculating the determinant:

$$\begin{vmatrix} 1 & 1 \\ 2 & -1 \end{vmatrix} = (1)\cdot(-1) - (1)(2) = -3,$$

which is a non-zero value.

How many young and adult insects? Cramer's rule

Cramer's rule is a theorem that makes it possible to solve systems of linear equations using determinants. The method was devised by Gabriel Cramer in 1750.



```
>>
>>
>> a=[1, 3, 3 ;
      4, -2, 1;
      1, 1,  2]
a =
     1     3     3
     4    -2     1
     1     1     2
>>
>> det(a)
ans =
    -8
>>
```

An intermediate stage in the application of the Cramer rule using the program MatLab.

The value of the unknowns is obtained by calculating the determinant of two types of matrices: D_j and D. The rule can only be used if the number of equations is equal to the number of unknowns, and the determinant of the matrix of the coefficients is non-zero ($\det(D) \neq 0$).

Let us see the Cramer rule in action in the entomology experiment. Given the system of linear equations:

$$\begin{pmatrix} 1 & 1 \\ 2 & -1 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix}=\begin{pmatrix} 180 \\ -6 \end{pmatrix}$$

let D be the matrix of coefficients corresponding to the system:

$$\begin{pmatrix} 1 & 1 \\ 2 & -1 \end{pmatrix}$$

where its determinant $\det(D)$ is equal to -3. Since the system has two unknowns, x and y, we have two matrices D_j: D_x and D_y. The matrices D_j are constructed by substituting a column j in D with the vector made up of the independent terms:

$$\begin{pmatrix} 180 \\ -6 \end{pmatrix}$$

In our experiment, and since x is the first unknown, j will be equal to 1. Substituting the first column of the matrix D with the vector made up of the independent terms, the matrix D_x is:

$$\begin{pmatrix} 180 & 1 \\ -6 & -1 \end{pmatrix}$$

where $\det(D_x)$ is equal to -174, since the matrix gives $(180) \cdot (-1) - (1) \cdot (-6)$. Following similar reasoning, and since y is the second unknown in the system of equations, with $j = 2$, the matrix D_y is:

$$\begin{pmatrix} 1 & 180 \\ 2 & -6 \end{pmatrix}$$

and the value of its determinant is -366, since $\det(D_y)$ is equal to the solution of $(1) \cdot (-6) - (180) \cdot (2)$.

Cramer's rule states that the solution to the system of equations is given by the following division of determinants:

$$x = \frac{\det(D_x)}{\det(D)},\ y = \frac{\det(D_y)}{\det(D)}.$$

Consequently, in the entomology experiment, we have:

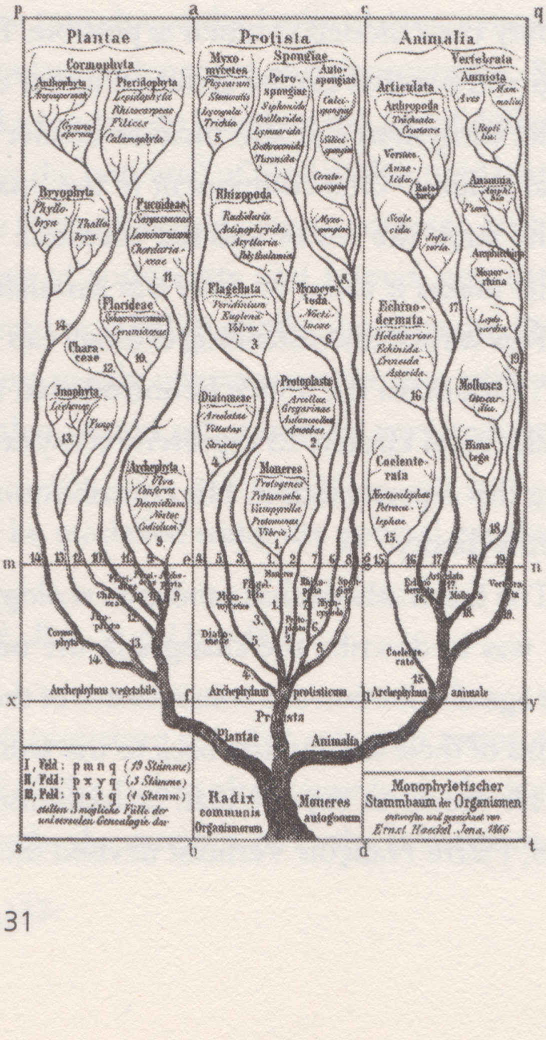
$$x = \frac{-174}{-3},\ y = \frac{-366}{-3},$$

meaning 58 young insects (x) and 122 adults (y) have been captured.

Chapter 6

Ecology and Mathematics: A Marriage of Convenience

In nature, living things – regardless of whether they are plants, animals, fungi or microorganisms – are not isolated but are related to each other and to the environment. In general, organisms from different species share a common natural space, referred to as an ecosystem. This is a given place or natural environment for which it is possible to distinguish certain non-living physical factors, which are referred to as abiotic on account of their 'non-biological' nature, from other biotic factors, which refer to the organisms that share the habitat. Abiotic factors include light, water, the temperature, the atmosphere or the soil and, in general, all the factors related to geology and the climate, whereas examples of biotic factors include plants, animals (herbivores and carnivores), fungi and bacteria.



Plantae
Protista
Animalia
Cormophyta
Bryophyta
Fucoideae
Florideae
Characeae
Inophyta
Archephyta
Myxomycetes
Spongiae
Rhizopoda
Flagellata
Diatomeae
Protoplasta
Moneres
Vertebrata
Amniota
Articulata
Arthropoda
Echinodermata
Mollusca
Coelenterata
Archephylum vegetabile
Archephylum protisticum
Archephylum animale
Radix communis Organismorum
Moneres autogonum
Monophyletischer Stammbaum der Organismen entworfen und gezeichnet von Ernst Haeckel Jena 1866

Ernst Haeckel (1834–1919) was the scientist who coined the term ecology. To his right, his design of the 'tree of life'.

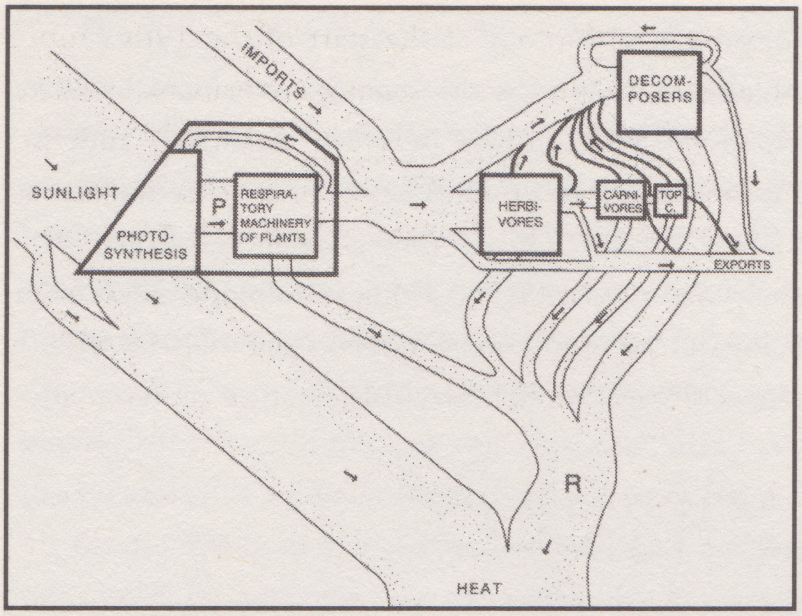
The discipline of ecology, born of biology at the start of the 19th century, studies ecosystems. The problems considered by this science are principally related to biodiversity, in addition to the relationships between organisms and their relationships with the environment. One interesting aspect of ecology is that since its inception, ecologists have felt the need to use mathematical biology to construct mathematical models that help them describe and predict ecological phenomena. This caused ecology to develop quickly, developing concepts and theories with the help of mathematics. Hence, ecological models are mathematical representations of ecosystems.

Building models

The transfer of energy between the organisms that inhabit an ecosystem takes place via food. The fact that some organisms eat others results in the formation of a food chain. One example of a typical food chain is plants → herbivores → carnivores → decomposers. In a mathematical model, each link in the chain is represented by, for example, the number of organisms, with the model describing features such as the flow of energy through the system. Since ecosystems are often considerably complex, both in terms of the number of species and their interactions, ecologists often simplify their models as much as possible. For example, in a model of an ecosystem, fungi and bacteria can be grouped into a common subsystem – decomposers. The model ecosystem can also include smaller models that combine to create the final grand scheme. One component of the final model is the environment, represented by the land, the sea or another medium. Clearly, the process of constructing the model makes it easier to carry out simulation experiments using a computer.

This way of understanding ecology can be largely attributed to the great ecologist H.T. Odum. In the 1950s he introduced the use of diagrams similar to those used for electrical circuits to represent ecosystems. Computer simulation is carried out using this representation. His contributions include the integration of ecology and systems theory.

The first mathematical models in ecology studied the dynamic of populations. The idea was to describe the changes in the number of individuals of a population and their age distribution as a consequence of their interaction with the environment. The origins of these studies date back to the work of Thomas Malthus in the 18th century and his model of exponential, or Malthusian, population growth. Subsequently, in 1938, Pierre François Verhulst devised the logistical model of growth.



Model based on the diagrams of H.T. Odum, whose innovative methodology represented a new way of studying ecosystems.

In the 1920s Vito Volterra and Alfred J. Lotka described two models that have become fundamental parts of mathematical ecology – the two-species competition model and the predator–prey model. Both models are of a similar structure but differ in that the two-species competition model assumes the growth of populations is logistic, whereas the predator–prey model assumes growth is exponential. Some 20 years later, in the 1940s, Patrick H. Leslie introduced the Leslie matrix, a model for population structure that combines population dynamics and demography. While the Malthus, Verhulst and Volterra–Lotka models are based on the use of differential equations, Leslie's advantage was to show the potential of models that used matrices.

Matrix algebra has shown itself to be a formidable tool when it comes to ecological modelling and simulating the dynamics of animal life and human populations. These matrix-based expressions are referred to as BIDE (Births, Immigrants, Deaths, Emigrants). An obvious advantage of using matrix operations is the ease with which computers are able to carry out tasks that would otherwise be very tedious and repetitive.

In a BIDE model, a population can be modelled using the general expression:

$$N_{t+1} = N_t + B + I - D - E,$$

where the number of individuals at a future time t + 1 is given in terms of the number present at t and the balance of all the factors that cause both the increase and decrease of the number of individuals: the number of births B between time

A BASIC BIDE MODEL

One of the most straightforward ecological models, based on matrix algebra, is described below. Imagine that we study a population of deer for which we know the number of young females of a non-fertile age N^J that survive S^J in an interval between time t and $t + 1$, as well as the number of adult females N^A that survive S^A in the same time interval, that is, between t and $t + 1$. If P^J is the percentage of young females that survive for each reproductive female, the population will evolve over the course of time in line with the following model:

$$\begin{pmatrix} N^J_{t+1} \\ N^A_{t+1} \end{pmatrix} = \begin{pmatrix} S^J P^J & S^A P^J \\ S^J & S^A \end{pmatrix} \begin{pmatrix} N^J_t \\ N^A_t \end{pmatrix}.$$

These elementary models make it possible to build other more complex models, such as that based on the Leslie matrix described at the start of this book.

t and $t + 1$, the number of immigrants I that join the population between time t and $t + 1$, the number of deaths D between time t and $t + 1$, and the number of individuals that emigrate E, leaving the population between time t and $t + 1$.

The Volterra–Lotka model: wolves and rabbits

During World War I, between 1914 and 1918, fishing was suspended in the north of the Adriatic Sea. When the conflict was over, fishing activities returned to normal. It was then, during the 1920s, that the Italian biologist Umberto d'Ancona carried out a quantitative study of the species of fish sold at the markets in Venice, Fiume and Trieste. D'Ancona's results showed that the markets sold more predatory fish than those that, due to their smaller size, constituted the natural food of these predators – their prey. D'Ancona was courting the daughter of a famous mathematician at the time, Vito Volterra. He suggested that the older man should carry out a mathematical study to provide a satisfactory explanation of the different number of predator and prey fish. His future father-in-law did just that and proposed a system of differential equations in 1926. A similar system had already been proposed a year earlier, although independently, by the American physicist and chemist Alfred J. Lotka. The results of their work is known as the Volterra–Lotka equations.

The system of differential equations that models the predator–prey relationship is one of the first models, and also one of the best known, in mathematical biology. It has clear uses in ecology when reintroducing species into a given geographic region, national park or zoo – deciding the number of fish that can live together in an aquarium together with predators, such as sharks. Furthermore, the model can also be applied in other areas, some of which include immunology, to describe the relationship between viruses and the immune system, or between cancerous cells and the immune system; parasitology, to describe the relationship between the host individual and a parasite; and even in economics, to describe the relationship between consumers and resources.

Let us provide an intuitive explanation of the meaning of this important model. In our model, let x represent the predators, such as sharks, wolves, etc., and y represent the prey, such as fish, rabbits, etc. We assume the predators only feed off prey, while the natural food for the prey is sufficiently abundant, regardless of its nature (plant-based, animals, etc.). Regardless of whether the relationship is between sharks and fish, or wolves and rabbits, the model is equally valid for thousands of predator–prey relationships, which can be between insects, protozoa, etc. However, the two relationships mentioned above are among the most popular.

To illustrate the model, we'll concentrate on the wolves–rabbits relationship. Imagine that the two populations were isolated from each other. This means the predators cannot feed off the prey, and consequently they will starve, leading to their death and causing the population of predators to decrease at a rate or rhythm determined by the following expression:

$$\frac{dx}{dt} = -px.$$

This is a simple differential equation in which the negative sign of p represents the mortality rate of the predators. Solving the differential equation gives the solution:

$$x(t) = x_0 e^{-pt}.$$

However, what does the equation given by the solution mean? In the expression, if x_0 is the initial number of predators (for example, the wolves that colonised a region some time ago), then, with the passing of time t, the number of predators

$x(t)$, and hence, wolves, will decrease rapidly, in an 'exponential manner'. This type of extinction is referred to as Malthusian reduction.

On the other hand, the prey (for example, rabbits) that is isolated from the predators and has sufficient food, will increase in number, with the population growing at a speed or rate determined by the following equation:

$$\frac{dy}{dt} = ry.$$

Note that this is a simple differential equation, similar to the one for the predators, except for the positive sign of r, which is the birth rate of the prey.

Solving the differential equation gives the equation for the solution, this time for the prey:

$$y(t) = y_0 e^{rt}.$$

As we can see, it conforms to the exponential or Malthusian growth model, whereby if y_0 is the initial number of prey (for example, the rabbits that have colonised a region), the number of prey $y(t)$ at time t will increase rapidly in an 'exponential manner' in line with Malthusian growth.

Let us now imagine that the two populations, predators and prey, coexist in the same region. What happens? The contact between predators and prey must be included in the expressions for the two populations when both are isolated from each other.

Consequently, in the expression for the speed or rate at which the population of predators changes, a term qxy must be included, which expresses their increase as a result of the 'contact' with the prey, where q is the parameter that models this contact. In line with the example, q can be defined as a rate related to the consumption of herbivores, specifically rabbits. This results in the following expression:

$$\frac{dx}{dt} = -px + qxy.$$

Note that the natural tendency towards extinction of the predators is compensated by increasing their number (from which comes the positive sign of qxy) as they feed off the prey. Consequently, the predators no longer die off and survive thanks to the availability of food, the prey.

Similarly, the natural tendency of the prey to unchecked growth is compensated for, with their number being reduced through the inclusion of the term $-sxy$ with a negative sign in the differential equation, where s is the parameter that models this contact. The term expresses their death due to contact with the predators, since these represent their food source.

$$\frac{dy}{dt}=ry-sxy.$$

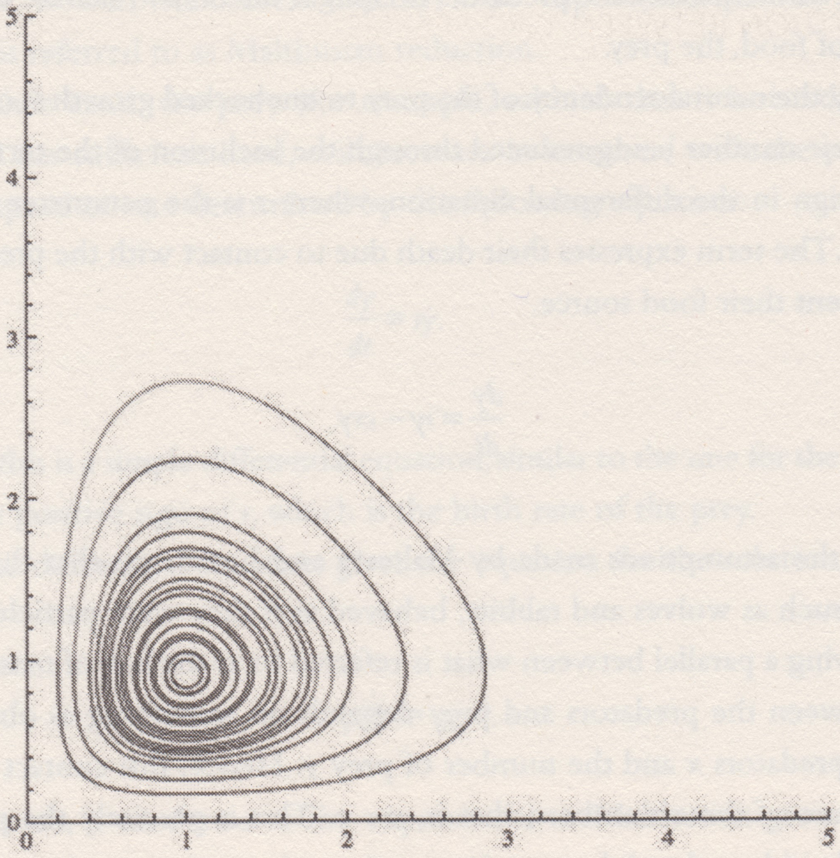
One of the assumptions made by Volterra and Lotka was that the individual specimens, such as wolves and rabbits, behaved as if they were particles of gas. Or rather, drawing a parallel between what is referred to as the law of mass action, the contact between the predators and prey depends on something as obvious as the number of predators x and the number of prey y. Hence, this contact is modelled as the product of these numbers, that is, $x \cdot y$. This is precisely the product that appears in the terms qxy and $-sxy$.

Bringing together the two differential equations in one system:

$$\frac{dx}{dt}=-px+qxy \text{ y } \frac{dy}{dt}=ry-sxy,$$

gives the famous Volterra–Lotka system of equations.

After including the terms that model the contact between the predators and prey, it is no longer as easy to get a solution to the system of equations, compared to when the populations were isolated. According to the model, the number of predators will increase if they have an abundance of prey (their food). However, as the prey is consumed the number of predators will also decrease. Similarly, owing to the decrease in the number of predators, the number of prey will start to grow again, which of course means that the number of predators starts to increase. This oscillating behaviour between predators and prey is such that representing the numbers of predators and prey on the same graph will give a cycle called the 'solution cycle', precisely because it is the solution to the Volterra–Lotka equations.



Volterra–Lotka predator–prey model: the number of predators appears on the Y axis and the number of prey on the X axis.

Based on this system of equations, there are processes of mathematical reasoning that lead to the solution cycle, but perhaps the most important is the idea of oscillation, in terms of both the number of predators and prey. The 'shape' of the cycle depends on the initial conditions, that is to say the number of predators and prey at the start.

Similarly, it is easy to calculate the point of equilibrium, since we know its coordinates are:

$$\left\{x=\frac{p}{q},\ y=\frac{r}{s}\right\}$$

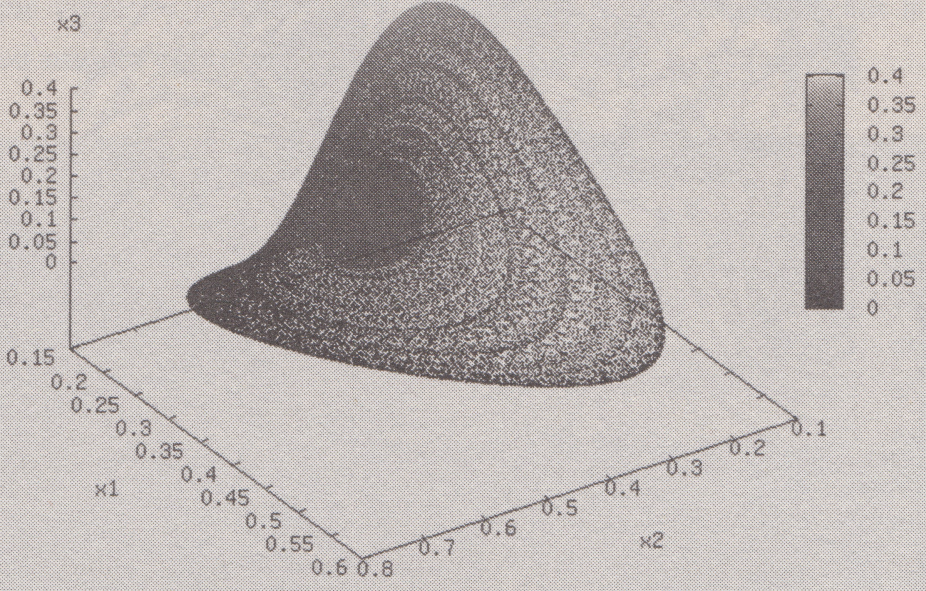
From now on, it will be helpful to bear in mind the idea of oscillating behaviour explained in this section, with respect to both predators and prey, especially when we come to discuss oscillations in climate models in the next section of this chapter.

COMPETITION BETWEEN TWO SPECIES

In addition to the Volterra–Lotka predator–prey model, the authors devised another model in which the relationship between two populations or species was one of competition. Let us imagine that two populations compete for the same resource with growth that is logistical. If x and y represent the number of individuals in each population, we have:

$$\frac{dx}{dt}=r_x x\left(\frac{k_x-x-\alpha_{xy}y}{k_x}\right) \text{ y } \frac{dy}{dt}=r_y y\left(\frac{k_y-y-\alpha_{yx}x}{k_y}\right)$$

where r_x, r_y are the growth rates of the species, and k_x, k_y are the carrying capacities for each of the populations. Similarly, the expressions include the interaction coefficients α, a parameter that models the interaction between the individuals of the populations. Hence, α_{xy} represents the effect of species y on x, while α_{yx} represents the effect of x on y. The model can be extended to handle more than two species, although the analysis of the situations becomes more complicated.



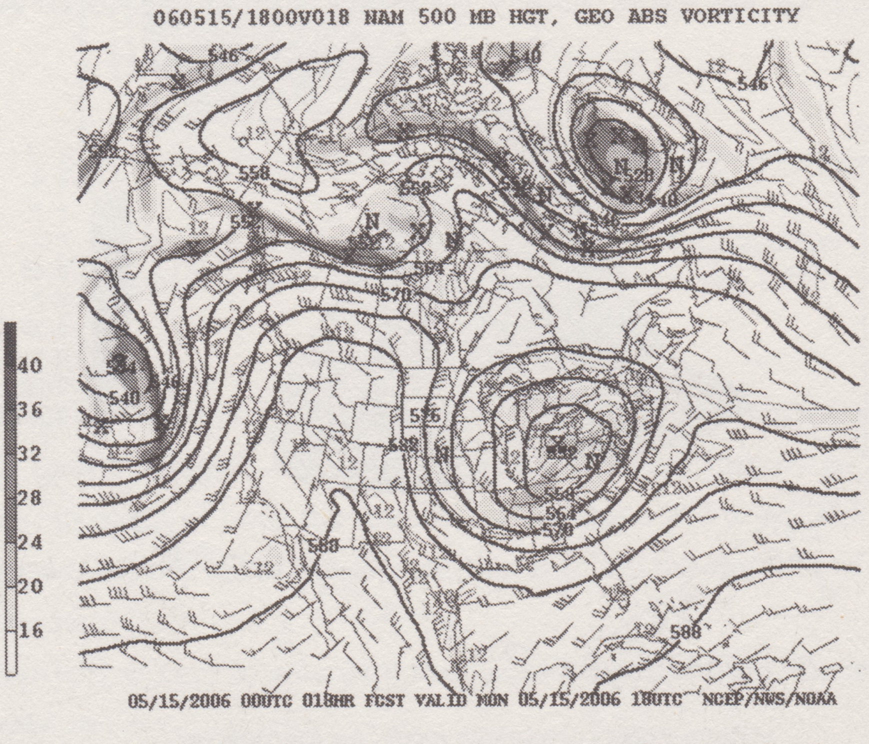
Volterra–Lotka competition model for four species.

Mathematical models of the climate: does climate change exist?

In recent years, the climate has become a hot topic. Every day the media provide information about the weather for that day and a forecast for the coming days. The work is carried out at weather forecasting institutes and involves complex mathematical models. However, it is not enough just to provide day-to-day forecasts.

Meteorologists have become involved in the need to study whether we are experiencing climate change or not.

The mathematical models used in meteorology are called climate models and are based on descriptions of the activity of the atmosphere and a computer simulation of the interactions between the atmosphere, the oceans, land and the poles. However, what do these models look like? Once again, they are models of differential equations based on the laws of physics. It is common practice to divide the planet into a grid, which is in turn divided into cells to which equations are applied. The meteorologist then calculates aspects such as wind speeds, relative humidity and the transfer of heat, as well as interactions with neighbouring spaces. They then make their forecasts based on their interpretation of the final results of the simulation.

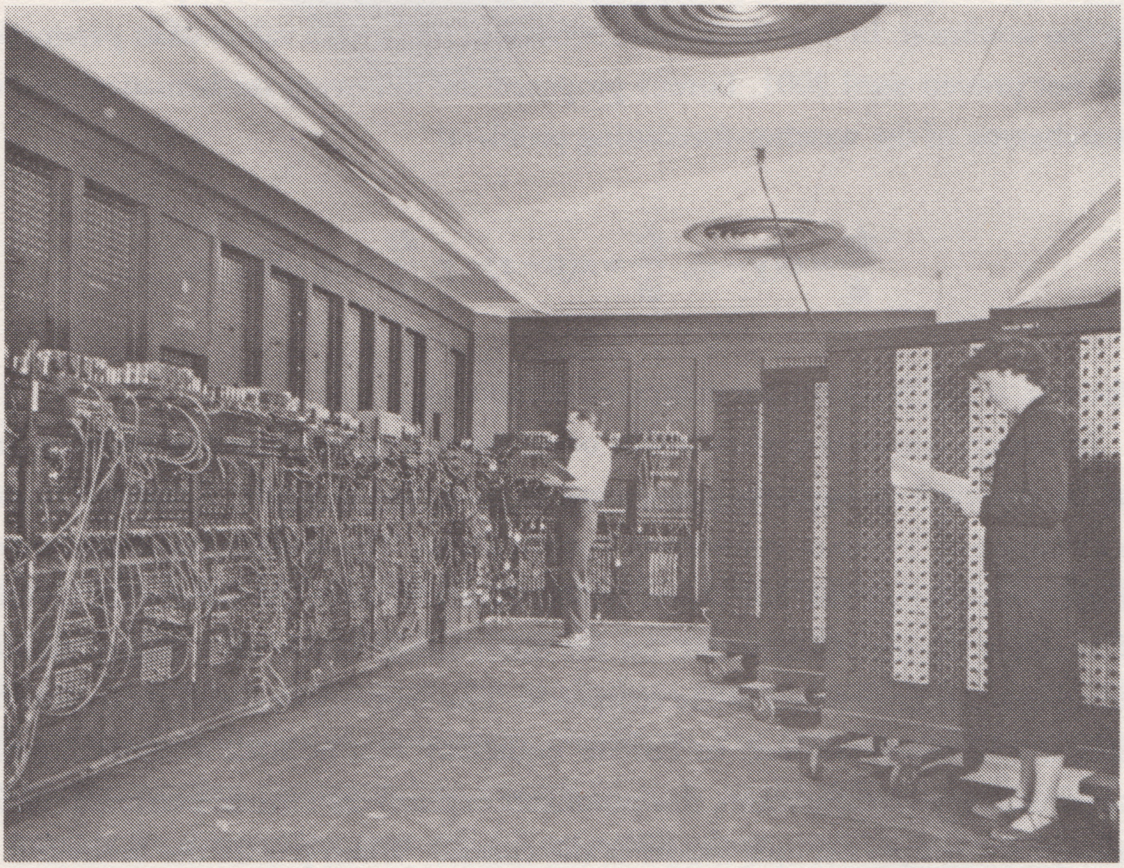

060515/1800V018 NAM 500 MB HGT, GEO ABS VORTICITY
40
36
32
28
24
20
16
05/15/2006 00UTC 018HR FCST VALID MON 05/15/2006 18UTC NCEP/NWS/NOAA

Mathematical models of the atmosphere make it possible to predict the weather.

Given that we now know the atmosphere is a chaotic system, it seems reasonable to ask how reliable these forecasts are. One of the most reliable sources of information used by meteorologists is 'climate regimes'. These are patterns of winds and other indicators that provide information about the weather to be expected (whether it will be sunny, cloudy, rainy, etc.). The regimes are obtained by applying statistical methods to historical records of the weather for countries or regions of the planet.

Problems of this nature led Edward N. Lorenz to study the atmosphere from the perspective of chaos theory. However, the first attempts to predict the weather took place prior to Lorenz' work in the 1960s. Jule Charney, Philip Thompson, Larry Gates, Ragnar Fjörtoff and the brilliant John von Neumann carried out experiments to predict the weather in the 1950s on one of the first computers in history, the American ENIAC.

Today, it is interesting to consider that at that time, a total of 24 hours of computing were required to predict the weather for the following day, and this is to say nothing of the accuracy of the forecasts. This is where we get the phrase "The climate is what you expect, the weather is what you get." The model that was used for forecasting represented the atmosphere as a grid with 270 points that covered locations in North America, separated at a distance of 700 km. Applying the finite difference method, ENIAC was used to solve differential equations and thus obtain forecasts. These pioneering scientists used a simplified model of the behaviour of the atmosphere to model the climate, based on the so-called barotropic vorticity equation. The features of this equation meant it could be calculated using a computer as primitive as ENIAC.



ENIAC and, in the foreground, Betty Zinder, one of its first programmers.

During the 1960s Lorenz worked at the prestigious Massachusetts Institute of Technology in the United States. For Lorenz the atmosphere behaved like a turbulent fluid and was highly sensitive to small changes. In order to make his experiment mathematically manageable, he designed a climate model that was as simple as possible, defining just three variables x, y, z. This means that for Lorenz, 'today's weather' is a point (x, y, z) in three-dimensional space. By extension, 'forecasting the weather for various days' would be the line or path joining the previous point to the others. Consequently, all the situations, or 'possible weather' are contained in what is known as the Lorenz attractor.

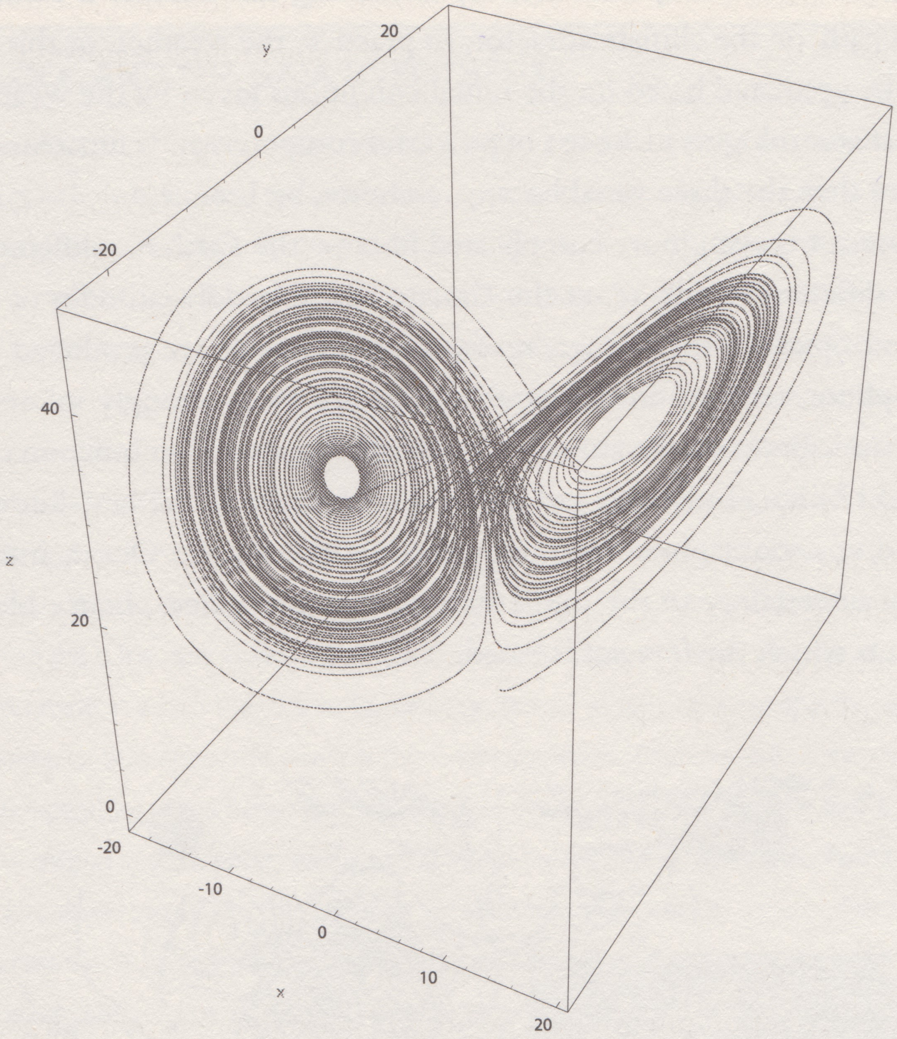
In 1963 Lorenz obtained three differential equations that he used to explain the convection movements of the atmosphere. The term *convection* refers to the movement of the molecules within a fluid, and is one of the main mechanisms for the transportation of mass and the transfer of heat on Earth. This means that Lorenz' equations are extremely important when it comes to the climate and weather forecasting. However, what is interesting about these differential equations is the fact that, in spite of the Earth's atmosphere behaving in an entirely predictable way (in principle), its behaviour is subject to abrupt and apparently random changes. This happens because, similar to the Volterra–Lotka equations, Lorenz' equations are also nonlinear. In fact, the chaotic behaviour for certain values of its parameters was not proven until 2001. Lorenz proposed the following mathematical model, an archetype of the weather-forecasting problem:

$$\frac{dx}{dt} = \sigma(y - x), \quad \frac{dy}{dt} = x(\rho - z) - y, \quad \frac{dz}{dt} = xy - \beta z,$$

where σ, ρ and β are the parameters of the model.

In nature, convection phenomena occur when a system becomes unstable, and can be observed through the movement of mass. For example, if water is heated in a receptacle, a heat or convection current forms. The result is the displacement of mass, in this case the hot water, which moves towards the surface on account of its lower density. Cold water, on the other hand, which has a higher density, moves towards the bottom of the receptacle. This type of phenomenon is classified using the Rayleigh number. In Lorenz' equations, that number is represented by the parameter ρ. Furthermore, this parameter explains the chaotic behaviour of the atmosphere in such a simple model of the climate. When ρ is 28 the behaviour of the atmosphere becomes chaotic.

From these observations, we can conclude that the Lorenz attractor is an oscillator that represents a three-dimensional model of the climate. In other words, as we have mentioned above, there are three variables involved, x, y, z, which exhibit a chaotic flow, evolving time and time again without repeating the pattern. Although this is a highly simplified model of the climate, the two large 'butterfly wings' of the attractor help to explain the behaviour of climate regimes.

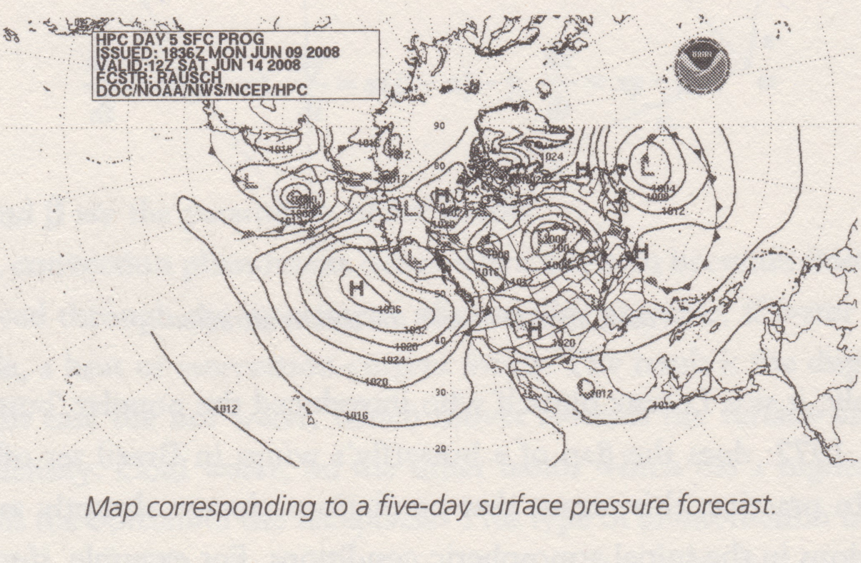


A basic climate model: the Lorenz attractor

Curiously, it was Lorenz himself who introduced the popular 'butterfly effect' concept in 1972: does the flap of a butterfly's wings in Brazil set off a tornado in Texas? In practice, this means that predictions change abruptly as a result of small variations in the initial atmospheric conditions. For example, if today in one location the weather corresponds to a point (x, y, z) on the right 'butterfly wing', the weather for the coming days will fall on a path whose origin is the point (x, y, z). The weather will be largely similar to the weather today if the path stays within the right ‘butterfly wing’. However, it may also be the case that the path evolves towards the left ‘butterfly wing’, radically changing the forecast.

The evolution of the weather along one path or another depends on the meteorological properties of the atmosphere ‘today’, referred to as the initial conditions in mathematical models. Hence, the path followed by the weather on subsequent days will depend on the initial conditions at point (x, y, z). In short, the weather is a chaotic system. Hence, forecasting the weather is forecasting ‘an individual path’ on the climate attractor. In practice, the weather, or this individual path, can be predicted based on the initial conditions given by the weather today. To do so, meteorologists make use of powerful computers and climate models with many more than the three variables x, y, z chosen by Lorenz.

The forecast is even more complicated because the Earth has different regions. It is quite different to talk about the climate in the middle latitudes of the planet and in the tropics. In the former, meteorological events are produced mainly by the atmosphere, whereas in the latter, events are more strongly influenced by a strong dynamic between the atmosphere and the ocean, a phenomenon commonly known as El Niño. Hurricanes and monsoons are some of the best-known effects. Furthermore, certain phenomena observed in the Pacific Ocean introduce an element of uncertainty to the initial state of the atmosphere, hence blurring the true state on which the forecast is based.



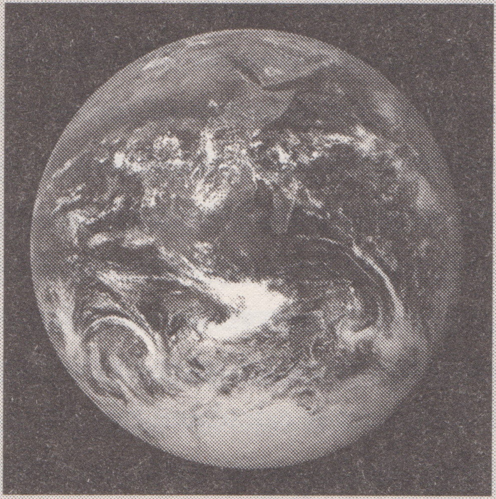
Map corresponding to a five-day surface pressure forecast.

Since 1963 – and thanks to Lorenz – we have known the difficulty of making reliable forecasts, precisely because of the chaotic nature of the climate. Therefore we use different mathematical models of the climate or different values for their parameters and initial conditions to allow meteorologists to produce different forecasts. It is then possible to evaluate the concordance or degree of coincidence between the various forecasts, hence obtaining an average forecast and a deviation or variance between forecasts. This method also takes into account the number of times a certain model of the set of models used is accurate in its predictions. This method, which makes use of a large set of climate models, instead of just a

LOVELOCK AND THE GAIA HYPOTHESIS

James Lovelock is an English researcher, born in 1919 and famous for his 'Gaia hypothesis'. According to Lovelock, living things are instrumental in maintaining the Earth's atmosphere and environment. Hence, according to his hypothesis, the Earth, the oceans, living things and the atmosphere form a cybernetic system. The idea of a cybernetic system was further pursued by the American researcher Lynn Margulis, who proposed that planet Earth is in fact a 'superorganism' that can regulate the conditions for evolution and sustaining of life.

However, the ideas of James Lovelock and Lynn Margulis had, and continue to have, their detractors. They were opposed from the outset by evolutionary biologists such as Stephen Jay Gould and Richard Dawkins. Such Darwinian evolutionists ask the question: is it not the environment that selects living things as predicted by Darwin's theory of evolution by natural selection? If this is the case, how is it possible to justify the claim that living things gradually modify the environment in which they live to favour their fitness? In spite of these objections, there are other examples that appear to confirm the Gaia hypothesis. Bacteria and algae maintain the surface temperature of the Earth; they also regulate the salinity of the seas and play a part in the storage of carbon in sedimentary rocks. According to the ecological hypothesis, their intervention in the environment takes place through what are known in cybernetics as negative feedback loops. One example that illustrates this type of mechanism is a home air-conditioning system. An increase or decrease in the temperature of a room is detected by a thermostat, which results in a response by the climate control system in the opposite direction, reducing or increasing the temperature respectively.



The Gaia hypothesis claims that the Earth is a cybernetic system on a planetary scale, a superorganism.

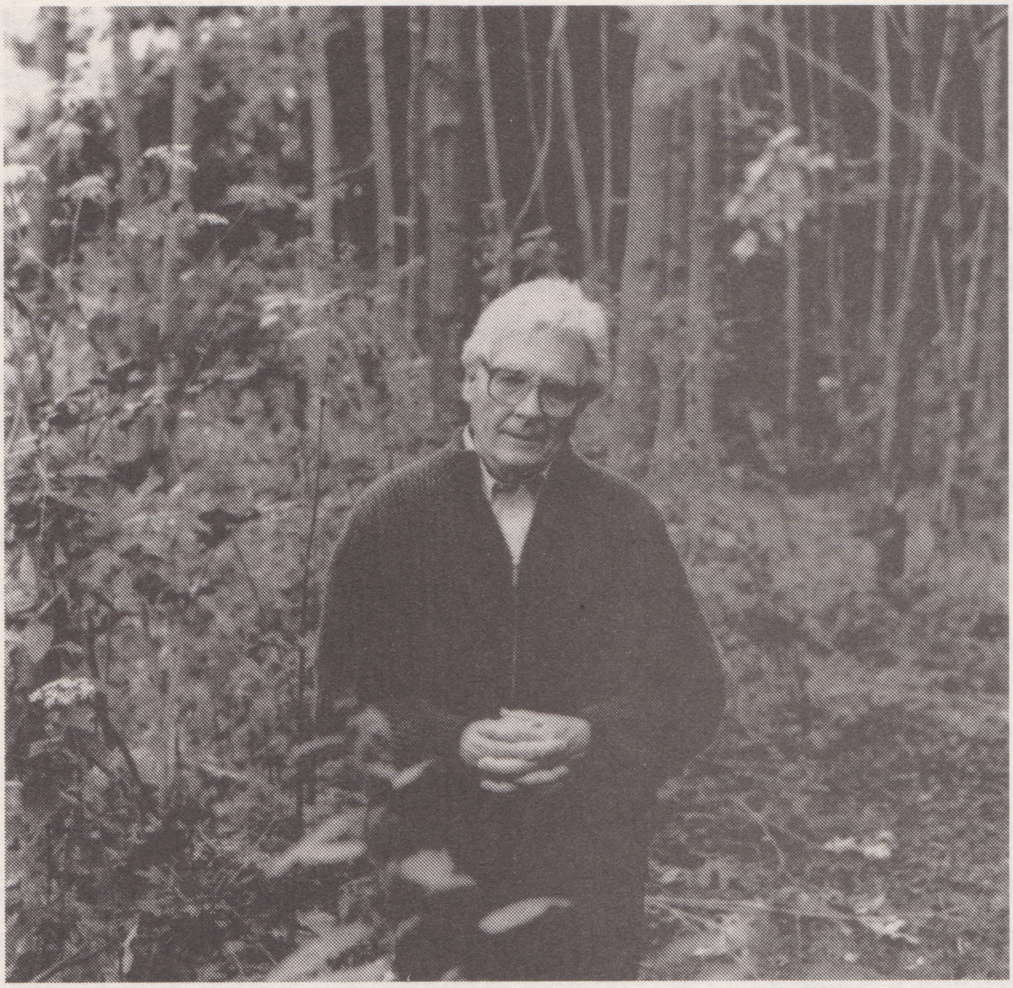
single one – as used at the time of John von Neumann and ENIAC – is known as a *multimodel ensemble*.

Finally, the question remains open: does climate change exist? Before beginning to tackle that question, we must define what is meant by climate change. From a mathematical point of view, it means a change in the shape and position of the climate attractor. This change can be caused by natural forces beyond our control, the actions of humans or a combination of both factors. Furthermore, if the change has occurred, is it significant, or is it just a small disturbance that affects an individual property of the attractor? It is probably too early to provide a definitive answer to this question. However, the action of living things can cause the climate to change. To make things even more complicated, at the start of the 1980s James Lovelock proposed the Gaia hypothesis, whereby living things maintain the composition of Earth's atmosphere. A simplified mathematical model based on Lovelock's hypothesis is Daisyworld, which we shall consider below.

And if we alter the atmosphere? Gaia and Daisyworld

Daisyworld is a mathematical model and simulation designed by Andrew Watson and James Lovelock in 1983. In a similar way to how Lorenz's equations provide a simplified model of the climate, Watson and Lovelock's model represented a simplified world inhabited by just two populations of daisies, one white and the other black. Their idea was to use a simple model to explain how living things can alter the environment – in this instance, the temperature of the planet. In principle, the underlying idea appears somewhat anti-Darwinian, since the living things' actions on the environment result in a more favourable habitat, hence improving their fitness.

The model assumes the existence of a sun with similar properties to our star, and hence, the presence of sunlight. It also considers the albedo, or the quantity of sunlight reflected by the daisies, both black and white, and the empty land where there are no daisies. Taking the albedo of the free land as a reference point, the white daisies reflect more light than the free land, and their local temperature is below that of the land. However the black daisies reflect less light than the land, meaning their local temperature is higher. In the Watson and Lovelock model, the balance of energy on the planet is calculated by taking into account the areas of the planet occupied by black daisies, white daisies and free space. Similarly, considering the mortality rate of the daisies, in addition to a mathematical function of the temperature, the model



James Lovelock, creator of the Gaia hypothesis, in a photograph from 1993.

establishes two differential equations that make it possible to simulate the growth of the number of black and white daisies on this imaginary planet.

$$\frac{dx}{dt} = x(\beta(T_x)S - \gamma), \quad \frac{dy}{dt} = y(\beta(T_y)S - \gamma).$$

These equations govern the rate at which the number of daisies increases or decreases over time. According to the first equation, the speed or rhythm at which the number of white daisies varies, x, depends on their number at time t, a growth factor $\beta(T_x)$, the fraction of the surface of the planet without daisies S, and their death rate γ. Note that the growth in the number of white daisies $\beta(T_x)$ depends on the local temperature T_x of the population of daisies.

Similarly, the second equation represents the dynamic for the population of black daisies. In this case y is the number of black daisies at time t, $\beta(T_y)$ its growth factor, which depends on the local temperature T_y for the black daisies, S is the surface of the planet without daisies, and γ is the death rate. Let us assume that γ is the same for both populations of daisies.

Let's note that the growth factor behaves in a similar way for the white daisies and the black daisies, exhibiting parabolic growth. According to this behaviour, the model arbitrarily assumes that the two classes of daisies have an average optimal growth temperature of 22.5 °C. Hence, when the temperature is optimal, the growth factor of the white daisies $\beta(T_x)$ and the growth factor of the black daisies $\beta(T_y)$ are highest and hence equal to 1. Given that the behaviour of the growth factors is parabolic, its value will drop to 0 as the temperature approaches 5 or 40 °C, values which have been chosen arbitrarily for the model. Hence, the growth factor will vary between 0 and 1 for the two classes of daisies and will be expressed in a similar way for the two populations, as shown below:

$$\beta(T_x) = 1 - 0.003265(22.5 - T_x)^2,$$
$$\beta(T_y) = 1 - 0.003265(22.5 - T_y)^2.$$

It is important to note that the temperatures in these expressions are local, and the number of daisies and hence the population may increase if the temperature is between 5 and 40 °C. Given that the white daisies reflect more solar energy, this will result in the 'cooling' of the region in which they are to be found. On the other hand, the black daisies absorb solar energy, causing the region to 'heat up'. The result of the different effects of the two classes of daisies means that the temperatures of the regions occupied by the white daisies T_x and the black daisies T_y can be expressed as:

$$T_x = Q\,(A - A_x) + T_m$$
$$T_y = Q\,(A - A_y) + T_m$$

where Q is the heat absorption factor (20 in the model) and T_m is the average temperature of the planet. In the expressions, A is the albedo of the planet, A_x is the albedo corresponding to the white daisies, and A_y is the albedo corresponding to the black daisies.

The average temperature of the planet, or rather the value of T_m on Daisyworld, is calculated using the Stefan–Boltzmann law. The law states that the energy radiated by an object is proportional to the fourth power of its temperature. Applying this law to the planet in our model gives the following expression:

$$T_m = \left(E_i \cdot \frac{1-A}{\sigma} \right)^{\frac{1}{4}} - 273,$$

where $\sigma = 5{,}669 \cdot 10^{-8}\ \mathrm{W/m^2 \cdot K^4}$ the Stefan–Boltzmann constant, and E_i is the solar energy received by the planet. Note that in the expression, if we wished to simulate a planet without life, or rather one not inhabited by daisies, the albedo value would be $A = 0.5$. The albedo of the planet A, or rather the quantity of light reflected by the planet is a function of how the surface of the planet is covered by the black and white daisies. This means that the albedo of planet A will be given by the following expression:

$$A = A_s \cdot S + A_x \cdot S_x + A_\gamma \cdot S_\gamma,$$

where A_s is the albedo of land without daisies that occupies a fraction of the surface of the planet equal to S; A_x is the albedo corresponding to the fraction of the planet's surface occupied by the white daisies, equal to S_x; and A_γ is the albedo corresponding to the fraction of the planet's surface occupied by the black daisies, equal to S_γ. Note that the expression for the albedo represents a model of the planet's energy balance. As we mentioned previously, the quantity of light reflected – or albedo – is lower for the black daisies than for the land without plants, and lower for the land without plants than for the white daisies, which can be expressed as follows $A_\gamma < A_s < A_x$.

The simplest simulation experiment with Daisyworld studies how the areas of the white and black daisies on the planet's surface increase and decrease. The standard values for the parameters of the model are $A_\gamma = 0.25$, $A_s = 0.50$, $A_x = 0.75$ and $\gamma = 0.30$. A planet with an abundance of white daisies will be colder than one with a majority of black daisies. In general, if the temperature of the planet increases, the temperature will decrease due to the effects of the larger proportion of white daisies, whereas any drop in the temperature of the planet will be compensated for by a larger proportion of black daisies. Furthermore, for certain solar constants there are two possible states of equilibrium: a planet without life or a planet covered with daisies.

Throughout the course of this book, we have undertaken a fascinating journey in which numerous examples have shown how biology and biomedicine owe part of their spectacular progress to a fertile relationship between mathematics and life sciences. The use of differential equations, chaos theory, symbolic calculation software and the ability to process vectors and matrices – and, in the case of the latter, the use of linear algebra – have allowed mathematicians to use mathematical expressions to describe the beauty and complexity of vital phenomena. Furthermore, mathematics allows scientists to build models that can be used to make computer predictions of the most wide-ranging aspects of life in the future, such as genes, proteins, cells, organisms, populations and ecosystems. We hope that this book has encouraged the reader to learn more about the study of mathematical biology, or biomathematics, a discipline with a long-standing tradition and future potential.

Appendix

The Magic of the Complex

For some strange reason, complex numbers underpin the ins and outs of many physical phenomena. For example, they are present in electromagnetics (used in electricity and electronics), quantum mechanics and wave behaviour, one example being the waves transmitted through water when we throw a stone into a lake. In mathematical biology, they are applied to the study of biological rhythms. Complex numbers are useful in chaos theory and essential for the graphical representation of fractals on a computer.

The graphical representation of complex numbers is simple. If we assume that a complex number is a point z, obtained using a Cartesian system of coordinates, which we shall call the complex plane, the horizontal axis X is used to represent the real part a, and the vertical axis Y is used to represent the imaginary part b. Furthermore, if we bear in mind that r is the distance from the origin to point z, it is easy to see that this distance, known as the modulus and written as $|z|$, is equal to $\sqrt{a^2+b^2}$. Furthermore, if we bear in mind that the real part a is the cosine, by definition the cathetus (leg or short side) adjacent to angle α, and b or the imaginary part, the sine or cathetus opposite angle α, multiplied by the modulus, in what is referred to as polar form the point z is equal to:

$$z = r(\cos(\alpha) + i\sin(\alpha)).$$

One of the most interesting properties of complex numbers is that they extend the possibilities for modelling reality, surpassing the limitations of real numbers. In order to handle them in a natural manner, it is useful to imagine that when working on the complex plane, the scientist has one foot in the real world (or part a) and another in the imaginary world (or part b). As required, they will travel from one world to another, hence exceeding the limitations of real numbers. In this way, for example, the addition and multiplication of complex numbers extends the meaning of these two operations, as we have seen in the study of two classes of fractals, the Mandelbrot and Julia sets.

The addition and subtraction of complex numbers

Addition and subtraction are operations that can also be carried out on complex numbers. Although at first sight it may appear difficult, the truth is quite the opposite.

The sum of two complex numbers, $a + bi$ and $c + di$ is equal to:

$$(a + bi) + (c + di) = (a + c) + (b + d)\, i.$$

For example, $(2 + 5i) + (3 - i) = (2 + 3) + (5 - 1)\, i = 5 + 4i$.

Subtraction is the opposite of addition, insofar as the subtraction of two complex numbers, $a + bi$ and $c + di$ is equal to:

$$(a + bi) - (c + di) = (a - c) + (b - d)\, i.$$

For example, $(1 + 3i) - (4 + 2i) = (1 - 4) + (3 - 2)\, i = -3 + i$.

The multiplication and division of complex numbers

In a similar way to other arithmetic operations, it is also possible to multiply and divide complex numbers.

The product of two complex numbers, $a + bi$ and $c + di$ is equal to:

$$(a + bi) \cdot (c + di) = (ac - bd) + (ad + bc)i.$$

Note that the result of the multiplication can be obtained in a more intuitive manner, operating as follows:

$$(a + bi) \cdot (c + di) = a \cdot c + a \cdot d \cdot i + b \cdot c \cdot i + b \cdot d \cdot i^2.$$

Remember that $i^2 = -1$, so:

$$a \cdot c + a \cdot d \cdot i + b \cdot i \cdot c - b \cdot d.$$

Reorganising the terms gives:

$$(ac - bd) + (ad + bc)i.$$

For example, $(2 + 6i) \cdot (8 + 2i) = (2 \cdot 8 - 6 \cdot 2) + (2 \cdot 2 + 6 \cdot 8)i = 4 + 52i$.

The quotient of two complex numbers, $a + bi$ and $c + di$ is equal to:

$$\frac{a+bi}{c+di} = \left(\frac{ac+bd}{c^2+d^2}\right) + \left(\frac{bc-ad}{c^2+d^2}\right)i.$$

For example,

$$\frac{3-5i}{6+2i} = \left(\frac{3\cdot 6-5\cdot 2}{6^2+2^2}\right) + \left(\frac{-5\cdot 6-3\cdot 2}{6^2+2^2}\right)i = \left(\frac{18-10}{36+4}\right) + \left(\frac{-30-6}{36+4}\right)i = \frac{8}{40} - \frac{36}{40}i.$$

Note once again that the quotient of two complex numbers is the result of carrying out the following operations:

$$\frac{a+bi}{c+di} = \frac{(a+bi)\cdot(c-di)}{(c-di)\cdot(c-di)} = \frac{a\cdot c - a\cdot d\cdot i + b\cdot c\cdot i - b\cdot d\cdot i^2}{(c-di)\cdot(c-di)},$$

such that reorganising the terms gives:

$$\left(\frac{ac+bd}{c^2+d^2}\right) + \left(\frac{bc-ad}{c^2+d^2}\right)i.$$

One of the most beautiful expressions in mathematics: Euler's formula

Complex numbers are not only useful for graphically representing fractals. They are also a common currency for engineers who work with electrical circuits. For example, while the power rating of a standard domestic appliance is measured using real numbers, the power rating of an industrial appliance is given in terms of complex numbers. In mathematical biology, the study of the biological cycles (the phases through which an individual passes) and in physics the study of oscillations (of an object hanging from a spring) share certain similarities, since complex numbers are used in both cases. This is why those who are familiar with these applications of complex numbers often use what is regarded as one of the most beautiful and useful formulae in mathematics. Although we shall avoid going into details, the expression is as follows – Euler's formula, which relates the imaginary number *i*, the powers of the number *e* and the trigonometric functions sine and cosine:

$$e^{\alpha i} = \cos(\alpha) + i\sin(\alpha)$$

It can be easily seen that on the complex plane, if we draw a circumference with a radius of one, the *X* axis will represent the cosine of angle α, whereas the imaginary axis *Y* will represent the sine of α. It appears that the formula was discovered and rediscovered on various occasions throughout the 18th century. In 1748 Euler discovered it through his work on power series, although nobody was able to represent it on the complex plane. The idea, which is so simple, of representing complex numbers on a Cartesian plane did not arise until later on, around 1800, thanks to the ingenuity of Jean-Robert Argand. It was not until then that we were able to see a graphical representation of one of the most beautiful formulae in mathematics.

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The Mathematics of Life

Numbers in biology and ecology

The life of the world around us may often seem to be a mesmerising chaos of shifting shapes: compelling, engrossing, but tumultuous. However, when we put on our mathematical glasses, in many instances chaos turns magically to order.
In this book, the reader can discover the key concepts of mathematical biology, illustrated with numerous examples and surprising applications from the real world.